A COMPARATIVE CLINICO-BIOCHEMICAL AND CYTOLOGICAL EVALUATION OF DIFFERENT TYPES OF HORMONE REPLACEMENT THERAPY IN POST MENOPAUSAL WOMEN.

THESIS
FOR
MASTER OF SURGERY
[OBSTETRICS AND GYNAECOLOGY]

BUNDELKHAND UNIVERSITY JHANSI
(U.P.)

2000 LALMANI

CERTIFICATE

This is to certify that the work entitled, "A comparative clinico-biochemical and cytological evaluation of different types of hormone replacement therapy in post menopausal women", which is being submitted as a thesis for master of surgery (OBSTETRICS AND GYNAECOLOGY) by Dr. LALMANI, has been carried out in the department of Obstetrics & Gynaecology, M.L.B. Medical College, Jhansi .

He has put in the necessary stay in the department as per University regulations.

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The results and observations recorded has been periodically checked and verified by me.

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ACKNOWLEDGEMENT

I am greatly indebted to my esteemed and learned teacher **Prof. Swadesh Sharma , M.S., FICOG Head of the Department of Obstetrics and Gynaecology**. She has given me her valuable advise and suggestions which played an important role in successful completion of the Present.

It is with due regards that I pay my gratitude to my most respected and learned teacher and guide , **Associated Professor Dr. Sunita Arora , M.S.,FICOG, Department of Obstetrics and Gynaecology**. Her keen interest untiring efforts constant supervision, constructive criticism and valuable help which she readily extended to me at every stage of this work.

I owe my sincere most thanks to my Co-guide **Prof. R.C. Arora, M.D. , D.Sc. , Head of the Department of Medicine,** for his untiring patience in explaining to me at length various aspects of work under taken in this volume without backing of his unlimited knowledge. I am sure it would have been impossible to complete such a project.

Words fail to express my gratitude to Co-guide **Dr. Navneet Agarwal M.D., Associate Professor Department of Medicine and Dr. Ratna Saxena M.D. Associate Professor Department of Pathology** , for their patients in

elucidating the various aspects of the work carried in this volume. Without their support and knowledge of various aspects of the subject it would have been difficult to accomplish the project for me.

I am also grateful to the faculty members of the department of Obstetrics and Gynaecology **Prof. M. Kapoor ,M.S., Dr. Sanjaya Sharma , M.D. and Dr. S. Kharakawal , M.D.**, for their constant encouragement and expert guidance during the study.

My sincere most thanks are due to **Mr. B.D. mathur, M.Sc., D.H.S., Associate Professor in Statistics and Demography, Department of Obstetrics and Gynaecology** for his help at every stage of work.

I deeply value the advice and moral support of my colleagues during this study.

I also pay my thanks to Sri Ashok Srivastava for his timely help in Serum Lipid Lipoprotein estimation.

I bow to my lady subjects who have formed the material for present study.

Mr. Rajendra Kumar Rai (Priyanka Computer & Graphics) deserve special thanks for carrying out this arduous task of programming, accurate manuscript performing the work skillfully, speedily and cheerfully.

Lastly I pay my regards to my friend Dr. Manish Dhingra for my moral support. It is a special pleasure to acknowledge the help extended and moral support of my younger brother, my friends, my Junior and Seniors , they always inspired my zeal and moral to build sufficient strength in me to complete this work. I sincerely dedicate my work to them.

Dated : 29/12/2000

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CONTENTS

INTRODUCTION

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Menopause is a natural and inevitable phenomenon and serves as an Objective sign of reproduction senescence. Although it is a normal event , various physiological and endocrinological changes occur due to ageing of the ovary and ultimately depletion of hormone levels , this leads to atrophy of various organs of body and produces various symptoms which affects woman's life adversely.

With increasing life expectancy menopause is a growing problem. It occurs earlier in cigarette smokers and in nulliparus women. High altitudes are found to accelerate menopausal age.

During the climacteric period women suffer from symptoms of vasomotor instablity such as hot flushes, night sweating, palpitation and insomnia etc, urogenital atrophy causes vaginal dryness, dyspareunia itching , Leukorrhoea , urinary incontinence , frequency , urgency nocturia and dysuria etc. Psychosomatic changes anxiety irritability, depression, insomnia. diminished libido etc. late consequences such as bony pain and spontaneous fractur.

In India, the age of menopause , varies from 44-50 years.

But approximately 8% of women undergo menopause before the age of 40 year or it may be delayed to 53 years.

Menopause is also associated with increase risk to coronary Heart disease due to adverse change in serum lipid and lipoprotein levels. Functioning ovary provide protection against coronary Heart disease because of estrogen production increase HDL concentration and reduce LDL concentration.

Artificially induced menopause may occur due to hysterectomy with or removal of both ovaries. Ovarian function may be suppressed by exposure to intense by exposure to radiation and inserting radium into the uterus. Induced menopause is more troublesome than natural one. Because the ovarian influence is withdrawn suddenly rather than gradually.

Previously, it was thought that menopause does not require any treatment. Most of the women adapt nicely to the physiological changes of menopause. But now-a-days this concept is totally changed. Current demographic trends indicate that due to increasing life expectancy and hysterectomies at an early age for various gynaecological problems , about 1/3 of women's life is in her post menopausal period. On the other hand women's are now playing increasingly active roles in the professional and social areas. Besides this , two aspects of modern life, urbanization

and migration have deprived elderly women of the traditional support from family and community , leaving them feeling insecure and vulnerable. It is, therefore, imperative to understand and manage the postmenopausal period by giving them hormone replacement therapy so as to allow women enjoy optimum health during these years.

Oestrogen deficiency ravages the health and well being of women at and after menopause. Hormone replacement therapy can offer relief. It can be given in variety of routes oral, transdermal, subcuteneous and vaginal.

Transdermal drug delivery system is a most recent achievement. It appears to be at least as effective as oral conjugated estrogen but allows a lower dose to be used , avoiding some of the metabolic adverse effects experienced with oral treatment.

Verious studies have indicated an increase in serum cholesterol level suggesting that lack of ovarian function particularly oestrogen is responsible for it or menopause or after oopherectomy. This concept has been greatly re-inforced by observations that serum lipid patterns and plasma cholesterol levels can be altered by administration of oestrogens .

Declining oestrogen level lead to increases rate of bone resorption and urinary excereti̇on of calcium resulting in reduced bone density or osteoporosis.

The present study is conducted to compare efficacy of different types of Hormone replacement therapy in post menopausal women.

AIMS AND OBJECTIVE

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1. To study the effect of conjugated equine estrogen, ostriol, levonargesterl and , ethinyl oestradiol combination (Ovral-L) and transdermal 17 Beta oestadiol in postmenopausal women.

2. To compare the efficacy of premarin, Evalon , ovral-L and transdermal E_2 Gel.

3. To evaluate the side effects and acceptability of the premarin , Evalon , ovral-L and transdermal E_2 gel.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

The term menopause, climacteric, peri and post menopause are used interchangeably applied to different stages at the end of reproductive years in the human female. Menopause is derived from the greek word men or month pause " To Stop" means cessation of menses, the climacteric or critical age is delivered from the Greek word "Klimacter" : Rung of the ladder and has been defined as transitory those in the life of human female between the age of reproductive and nonproductive ability (first : International congress on the menopause, 1976).

As the climacteric is regarded primarily as estrogen deficiency syndrome but typical complains. However those are which begin when estrogen production decline or stop. It occurs either spontaneously in the perimenopausal period or enforced after bilaterl oophrectomy. These symptoms are likely caused directly or indirectly by estrogen withdrawal and they can be treated successfully with estrogen substitution called as hormone replacement therapy.

However replacement therapy is available in many formulation combination and routes. Oral route, various routes of H.R.T. are also available such as subcutaneous

implants, percutaneous gel, vaginal ring and pessaries and transdermal device. Since no single product or regimes can be prescribed to all women or aplpliciater of these option and explain the therapeutic choice of patience and physician.

Menopause occurs at a mean age of 51 years. The most significant symptom of menopausal transition in some women is menstrual irregularity (Mc kinley S.M. , Brambille 07 Posner JG - 1992

Cardivascular disease is a major cause of morbidity and death in modern society and leading cause of death in older women with a incidence that approaches that in men of comparable age. The risk factors include cigarette smoking, male sex, advancing age and elevated blood lipid contents, elevated blood pressure and alteration in lipoprotein metabolism are major contributors to cardiovascular disease in general and to coronary heart disease in particular.

Age and Sex as Risk Factor For CVD

Women develop CHD much less frequently than men however sex difference decreased with advancing age possibly due to menopause.

Oliver and Boyd (1955) showed that combined effects of cholesterol and blood pressure are powerful contributors of CHD both in men and women but at any level of risk factors

singly or in combination women were at low risk, that men of same age group but this incidence decreased with advancing age.

Sperry and Webb (1950) showed that age itself is a risk factor for CVD due to associated increase in cholesterol and triglycerides.

Menopause and Cardiovascular Disease

Snazzerdan and Oliver (1963) showed that premature spontaneous menopause was associated with increased incidence of ischaemic heart disease.

The Framingham's study by william B Kannel et al (1976) showed that comparison of the incidence of cardiovascular disease at specified ages showed upto 55 a two fold increase among post menopausal versus pre-menopausal . The impact was greater on younger ages than older both with surgical natural menopause. Same was observed by Hjortland et al.

Castelli WP et al (1977) and Miller (1987) showed that the levels of high density lipoprotein were lower in persons with CHD than in those without the disease. It was found in most age , race , sex specific groups. The inverse HDL cholesterol CHD association was not appreciably diminished when adjusted for levels of low density lipoproteins and triglycerides.

LDL, total cholesterol and triglycerides were directly related to CHD prevalence.

Gordon et al (1978) showed that there was increased risk of CVD associated in women under 45 associated with natural or surgical menopause.

Rosenberg et al (1981) evaluated the relation between age at menopause and the risk of ischaemic heart disease. It showed that women oopherectomised before age of 35 years were at 7.2 times risk that of premenopausal women. Hysterectomy without oopherectomy was only weakly associated with increased risk.

Colditz et al (1987) showed that women who had undergone bilateral oopherectomy had increased risk of coronary heart disease as compared to premenopausal women.

Effect of Gonadal Steroids on Plasma Lipoproteins and Individual Phospholipids

The lower incidence of coronary heart disease has lead to many to believe that endocrine factors are of importance for the homeostasis of lipids in the plasma but also for the deposition and metabolism of lipid in the vessel wall.

Oliver and Boyd (1955) showed small but significant changes in the plasma lipid levels occur during menstrual cycle which is correlated with the varistions that occur in the hormonal secretion.

Kim and Kalkaff et al (1981) showed from menarche to menopause in a female there in 10-15% cycle suppression of plasma cholesterol, LDL, LDL alpha , beta during luteal phase while HDL cholesterol increases during other second half of the cycle.

Effect of Natural or Surgical Menopause on Lipoprotein Metabolism

Lipid metabolism is an important aspect of liver function which is apparently influenced by oestrogen and progesterone. In circulation lipids, which are insoluble in water are transported within special carriers particles called lipoprotein. Lipoprotein contains hydrophobic glyceride and cholesterol esters molecules covered with a surface monolayer of phospolipids esterified cholesterol and specific proteins. The apolipoproteins, the lipo proteins are separated into density classes according to their relative amount of lipid and proteins. They are divided according to their density into low density lipoproteins, very low density lipoproteins and high density lipoproteins.

Low density lipoproteins and very low density lipoproteins particles can be described as carriers to peripheral tissue. The high density lipoproteins containing about 50% of proteins are at present regarded as cholesterol regulators which transfer cholesterol from peripheral tissues including vascular endothelium to the liver. Subsequent excretion of cholesterol through bils and biochemistry involved plasma enzymes lecithin cholesterol acyl transferase. HDL has also been suggested to block peripheral LDL receptors thereby reducing cholesterol uptake and storage in endothelial cells of vassals. The development of atherosclerosis is dependent on many factors excess storage of cholesterol in arterial wall is however of major importance in this event and an impairment of HDL levels might thus accelerate this process.

1- Serum Cholesterol

Oliver and Boyd (1959) showed that there was significant rise in serum cholesterol by ovariectomy.

Sznajderman and oliver (1963) showed a significant rise in serum cholesterol in women with premature menopause those compared with pre-menopausal women of same age group.

Arnold and Ritterband et al (1963) showed that levels of serum cholesterol was significantly higher in oopherectomised than those of hysterectomised women.

William and Kannel et al (1976) also showed increased serum cholesterol level menopausal women than pre-menopausal women.

Pansini et al (1984) showed that there was steady rise in serum cholesterol value in women with bilateral ovariectomy within 6 months of operation.

Farrish et al (1990) showed significant increase in cholesterol level ($p<0.05$) in 6 months of operation from a mean of 3.57m mol/l to 4.21m mol/l.

2. *Serum triglyceride*

Oliver and Boyd (1959) showed a significant elevation of serum triglycerides in bilateral oopherectomised women.

Sznajderman and Oliver (1963) showed that serum triglycerides were significantly raised ($p<0.01$) in study group of women with premature menopause as compared to healthy woemn of same age group but there was not significant fall in the level after menopause.

Aitken et al (1971) showed a significant rise in serum triglyceride with age. However, the levels of serum triglyceride in oopherectomised had slightly lower values but was statistically not significant.

Punnonen and Rauramo (1976) showed that the serum triglycerides level rose significantly ($p<0.01$) after 1 months of bilateral oopheractomy.

Pansini et al (1984) showed no significant rise in triglyceride level within 3 months of bilateral oopheractomy.

Notelovitz et al (1983) showed that serum triglyceride levels were higher in oopherectomised women (71%, $p<0.02$).

Farrish et al (1990) showed no significant rise in serum triglyceride level in bilateral oopherectomised women.

3. *High Density Lipoprotein*

High density lipoprotein particles transport cholesterol from peripheral tissue including vascular endothelium to liver where it is metabolised and excreted through bile. An impairment of high density lipoprotein will accelerate excess storage of cholesterol in endothelium of arterial wall one of the factors leading to development of atherosclerosis.

The lower the high density lipoprotein level there is higher the risk of etherosclerotic manifestation HDL is heterogenous group and has got two main subfractions HDL_2 and HDL_3. Low levels of HDL_2 are clearly related to high risk of atherogenesity while total HDL and HDL_3 are not.

William and Kannel (1976) showed that serum HDL level is higher in women than men, but no discernable change in alpha fraction with menopause.

Punnonen and Rauramo (1980) showed that HDl cholesterol levels before and one month after castration did not differ significantly.

Notelovitz et al (1981) showed that HDL levels in oopherectomised women were 27% lower than in intact women.

Pansini et al (1984) showed that HDL cholesterol has biphasic dependence on time with initial decrease and later significant increase during the later 3 months.

Farrish et al (1990) measured HDL subfraction to assess any change in relative amounts of cholesterol carried on HDL_2 , HDL_3. No significant change was found in either fraction.

Low Density Lipoprotein and Very Density Low Density Lipoprotein

LDL and VLDL are directly related to atherogenesity of person and hence their elevated levels are also reported with conditions favouring atherogenesis. The values of LDL are calculated from standard formula. VLDL is 20% of the serum triglyceride. VLDL is supposed to carry triglycerides found in the liver or possibly in the intestine to body tissues where

triglycerides and fatty acids are hydrolysed by lipoprotein lipase enzyme. Metabolites are used for energy during the metabolic process and remanants left behind are taken by liver and converted to LDL. Accumulation of remanants favours atherogenesis and oestrogens reported to enhance the removal of remanants.

Arnold and Ritterband et al (1963) showed that mean serum cholesterol and percent of beta lipoprotein in oopherectomised women under 50 were higher then the hysterectomised women.

William and Kannel et al (1976) showed that cholesterol level in the prebeta fraction and beta fractions for women rises repidly while remaining essentially unchanged for men older than that age range.

Pansini et al (1984) initial declined then increased in apoprotein B levels the main carriers of LDL and VLDL fractions a significant increase upto 12.5% of the pre-operative value.

The rise in LDL cholesterol value showed tendentious increase without variation the 5% level.

Farrish et al (1990) showed a significant rise in LDL cholesterol ($p<0.05$) in the 6 weeks after operation from a mean of 3.57 m mol to 4.21 m mol/l.

Effect of Hormone Replacement Therapy in Post Menopausal women on serum lipid

Increasing age has an influence upon circulating lipid levels. Both cholesterol and triglyceride concentration increases with age and there is augmented risk of atherosclerotic disease. Increased cholesterol level is associated with increased LDL and VLDL levels. HDL carrying 20% of cholesterol has a cardioprotective effect.

Of the two major subfractions of HDL cholesterol the HDL_2 is associated with reduced risk of cardiovascular disease diseases. The higher HDL concentration in females is due to higher HDL_2 concentration. Various studies have shown the blood lipid changes associated with oestrogen LDL cholesterol.

Experimental work by Imai et al (1980) indicated that it is not free cholesterol that causes intimal vessel damage but rather abnormal oxidation product of cholesterol then it can be assumed that young ovariectomised owmen are at greather risk of cardiovascular disease due to oestrogen deficiency.

Aitken (1971) showed that administration of 20-40 ug of mestronol daily in oopherectomised women was associated with significant fall in serum cholesterol and a significant rise in serum triglycerides.

Gustoson and Svanborg (1972) : an oestrogenic steroid was given for three weeks period to 6 oopherectomised women. There as significant rise in HDL and VLDl and decrease in LDL levels.

Punnonen and Rauramo (1976) showed that administration of 2 mg estradiol valerate in oopherectomised women showed significant rise in serum phospholipids but no significant effect on cholesterol and triglyceride levels.

Patterson et al (1980) showed that there was little alterations in the mean serum cholesterol concentration and triglycerides with cyclical oestrogen but sequential oestradiol valerate and norgestrel significantly reduced the mean serum cholesterol and significant rise in serum triglyceride in post menopausal women.

Punnonen and Rauramo (1980) showd that injections of both 10 mg of oestradiol valerate and 2.5 mg of estradiol benzoate plus 10 mg estradiol thenyl propionate caused significant rise in HDL cholesterol level in bilateral oopherectomised women.

Notelovitz et al (1983) : different types and doses of oestrogen was administered in bilateral oopherectomised women. After 3 months serum cholesterol levels were unaffected by 1 and 2 mg of micronized 17 beta oestradiol or 0.625 and 1.25 mg of conjugated equine oestrogen.

Triglyceride levels were significantly elevated with conjugated oestrogen administration. A trend towards higher relative protein of high density lipoprotein and lower relative proportion of low density lipoproteins was observed in all.

The writing group for PEPI Trial (1995) It was demonstrated that there is a decreased in total cholesterol, an increasing in HDL level by about 10% , and decreased in LDL level also by about 10% on unopposed oestrogen for HRT.

Darling et al (1997) When HRT in pharma continuous conjugated equine estrogen with medroxyprogesteron acetate 5 Mg was compare with simvastatin , both caused a similar degree increase in HDL level.

Menopausal Symptomatology

According to Levgaten & Kraines (1966) Symptoms of menopause may begin in perimenopausal period, maximum of compleicts usually 2-3 years menopause and then slowly decreases.

The climacteric refers to the period before and after menopause during which Ovarian activity is diminished and gradually ceases. This period may manifest as short term syndrome and long term complications ,while short term syndrome must be treated and long term complications must be privented.

The climacteric syndrome includes early (Stage 1early symptoms, intermediate (Stage II) and late symptoms (Stage III) and complication.

Stage - I Early Symptoms :-

Vasomotor Instability : Hot flushes , night sweating , vertigo palpitation and weakness.

Stage - II Intermediate Symptoms :-

a. ***Urogenital atrophy*** :- Such as atrophy of vagina breast and urethra etc. Symptoms produced by this, are vaginal dryness , pruritis ,discharge , dyspareunia and urethral syndrome such as stress incontinance, burning , frequency & urgency etc.

b. ***Psychosomatic changes*** :- Anxiety, Irritability ,depression , insomnia , sexuality changes , diminished libido.

Stage - III Long term Complications :-

- ***Osteoporosis*** :- Presented as Bony pains and spontaneous fracture.
- Ischaemic Heart Disease.
- Cardiovascular changes.

Stage I Vasomotor Instability :

Hot flushes : Patients complains of Intense heat felt most commonly on the face the arms and the upper part of body. The hot flushes is inturn followed by profuse sweating and

often accompanied by palpitation, Dizziness, Axiety and Insomnia or sleep disturbances.

It is often the earliest and most common climacteric symptom presents in 60-80% of perimenopausal and post-menopausal female, Average duration of hot flush is the minut. Frequency of the flush varies from few episode per week to several episodes per hour. Hot flush can occur at any time in day or night. Hot flushes are the Episode of inappropriate heat loss. During flush skin temperature may rise by 5^0C these hot flushes are accompained by vasodilatation and elevation of levels of leutenizing hormones.

Symptoms of vascular instability subside by itself within 2-3 years.

According to Novak typical climacteric symptoms in this series are only the vasomotor complains. It Namely hot flushes and profuse sweating often. accompanied by dizziness , palpitation and tingling in upper extrimities.

According to Utian palpitation sometimes occurring at the same time at hot flushes age apprentally, not directly caused by oestrogen deficiency.

Stage II - Intermediate Symptoms :-

a. Symptoms due to urogenital atrophy :-

Atrophic changes occur with greater severity in tissues with a preponderance of estrogen receptors , which have been

detected in abundance in the human vagina and uterus , which are considered prime hormonal torget organs. High concentration of estrogen receptors are also found in distal ureter and trigone of the bladder.

Recent studies have found hormone receptors in women in pelvis musculature like the levetor ani and Urogenital ligaments like round lagament (Smith et al 1990).

Vaginal Symptoms :-

Low estrogen levels result in thining of the vaginal epithelium , decreased vascularity and loss of elasticity. The epithelial cells remain immature, their glycogen content reduce and pH increases. The predominant symptoms resulting from these changes are senile vaginitis, vaginal dryness, itching and dyspereunia. Dyspareunia and vaginal dryness lead to decreased sexuality in females.

According to Raz R, stamm M. (1993), vaginal symptoms include dryness , dyspareunia, and recurrent vaginal infections Fortunately , these symptoms are reversible with estrogen therapy.

According to Houser et al (1981) vulual atrophy sometimes accompanied by pruritis and burning , is certainly a sign of estrogen deficiency.

Urinary Complaints :-

Recurrent III, Burning, frequency , urgency nocturia etc. genuine stress urinary incontinance may be related to estrogen deficiency.

Atrophy of distal urethra and stenosis ultimately causes outflow obstruction.

Stress incontinence - Estrogen receptors are found in distal part of urethra. Post menopausal changes lead to atrophy of mucosa, decreased vasculerity and diminished tone of urethral muscles result in recurrent attack of UTI and stress incontinence. In stress incontinence patient complaining of passage of urine with coughing , snizzing and laughing. This is socially embarrassing situation (Reckess et al 1992).

b. Psychological Symptoms :-

Psychological symptoms such as axiety, irritability , depression & insomnia are most common , just before the onset of menopause.

Falling estrogen level are directly related to mood changes and psychosomatic symptoms vasomotor symptoms often lead to sleep deprivation , chronic fatigue and hence related to psychological symptom such as depression , irritability and mood changes.

Social factors like breavement, departure of children from home and changing circumstances may contribute significantly to menopausal psychological effects.

Stage III - Long Term Complication :-

a. *Cardiovascular disorders :-*

Hypertension and atherosclerosis increase in women after menopause and leads to increase incidence of ischemic heart disease.

Menopause increased risk to coronary disease due to adverse changes in serum lipids and lipoprotein levels and the declining estrogen levels.

Although the risk of death from coronary artery disease is at least three times as great for men as for women before menopause the relative rish for women increases significantly after menopause.

b. *Osteoporosis* :-

A sudden decrease in the gonadal hormones estrogen and progesterne as seen after oopherectomy or with the onset of amenorrhoea , is associated with dramatic changes in the remodeling of bone, resulting decrease in trabecular bone and predispose the person for spontaneous fracture.

Symptoms produced by these changes are body pain , backache loss of weight , kyphosis , wrist fracture after minor frame and spontaneous fracture of long bones.

Numerous biochemical demonstration has shown that estrogen probably inhibit the activity of osteoclast and may render a negative calcium balance by inhibiting the loss of calcium via urine and feaces.

According to peck W.A. (1990). Bone loss after menopause in exggerated to a rate of 3-5% per year.

This loss is most rapid during the first 5 years after menopause , when up to 201 of the expected lifeline loss from the femoral neck may occur (Hedlund LR , Gallagher, J.C.1989).

Other Symptoms :-

Skin changes Estrogen receptors are also found in skin and collegen tissues. In menopausal period , due to decrease in estrogen receptor, skin becomes dry and wrinkled. Due to increased production of melanin, complexion becomes dark usually patients of high class society or professional ladies present with this cosmetic problem.

Changes in vaginal Smear following Menopause :-

The most sensitive parameter of estrogen action on the vaginal epithelium is vaginal cytology. In post menopausal

female , apathic changes occur in vaginal epithelium. It is one of most practical , reliable and economical test available. The cytologic finding in menopausal patients may show awide spectrum of changes ranging from persistent or elevated estrogenic pattern to one of complete atrophy.

Vaginal squamous epithelium consist of three layers superficial layer, Intermediate or parabasal and basal layer. Superficial layer is estrogen dependent. In menopause low estrogen levels result in thinning of the vaginal epithelium decreased vascularity and loss of elasticity. The epithelial cells do not undergo maturation, those glycogen contents reduce number of vaginal lactobacilli decrease and vaginal pH increases and predispose vagina to secondary infection. Vaginal smear consisting of Intermediate and parabasal cells with the Karyopyknotic index and low maturation index.

Hormonal changes following menopause :-

In human ovary, there is a continuous and progressive decline in the number of follicles from total life onwards this loss can not be accounted for by ovulation alone, since the reproductive life in 30-35 yeas in women can only account for a loss of 350-450 follicles. All types of follicles small , medium and large show decline in number with age , continuously through a process of atresia also.

Progressive decline in the number of ovarian follicles is responsible for decreased production of ovarian inhibin (Mc Lachlan et al 1988).

Ovarian inhibin is non-steroidal water soluble protein secreted by granules cells of graffian follicle under the influence of estrogen. It suppress the pituitary follicle stimulating hormones by negative feedback mechanism.

Reduce number of ovarian follicales leads to decreased estrogen production and ultimately decreased inhibin production so there is loss of negative feed back mechanism and ultimately FHS increases in blood.

In the menstruating women , FHS , on cycle days should be 5-10 IU/L with normally functioning ovaries , Elevated FHS levels (10-25 IU/L) suggest relative ovarian resistance consistent with menopausal transition FHS (evels > 40 IU/L are consistent with complete cessation of ovarian functions.

Prior to menopause , LH levels are usually in the range of 5-10 IU/L. LH lvels increases in the menopausal transition in a manner similar to FHS.

So first detectable endocrine manifestation is a gradual increase in plasma follicle stimulating hormone. Sometimes after the rise in FHS , estradiol level decreases slightly and serum LH , increases Eventually as estradiol secretion falls to

very low level both FHS and LH rise to post menopausal level and remains elevated.

Harmone Replacement Therapy :-

Estrogen deficiency has been considered by many to be a physiological rather than pathological condition , probably because ovarian failure is genertically programmed. With the increased life deficiency becomes more significant. Hormonal changes induced by ovarian failure can influence health adversely , even in those who do not develop obious menopausal symptoms ,continuing changes even eventually lead to serious age related desorder such as osteoporosis.

In symptomatic menopausal female hormone replacement therapy provides certain relief. Beside this short term benefit , hormone replacement therapy now has an established role in prophylaxis against osteoporosis and cardiovascular disease, thereby lowering morbidity and mortality rates.

With increasing life expectancy and heightened health awareness , women now seeks the prevention and cure of the problems and have expectations of long term good health. It is therefore , Imperative to understand and mean age the post menopausal period by giving them HRT, so as to allow her to enjoy optimum health during these years.

Although "Lilandwlar therapy" for various ailments may be traced back to Egyptian times, the first suggestion that

ovarian secretion could be used to treat symptoms of ovarian failure was made in 1885 by mariebra. The therepeutic prepration of that time included grass ovarian tissue, Ovarian Juice and powdard ovaries.

In 1923 , Estrogen was first isolated from procaine follicular fluid by Allen and Doisy.

In 1931 , they were discovered to be abundant in the urine of pregnant mares.

In 1938 , the synthetic estrogen diethyl stiboestral and ethnyl estradiol were developed.

During 1930s , and 1940s estrogen although very expensive and minimally efficacious when administered oraly , were used to suppress lactation after parturition and to treaevere menopausal symptoms. In long term clinical studies of estrogen use in men were being because of theoretical cardiovascular benefit.

In addition , in 1960s many advocate life long estrogen therapy for menopausal women to keep them feminine formen during this time oestrogen use increased tremendously, with little regard to adjustment of dose of selection and patient.

The fact remained , however , that many women had diabing symptoms, related to estrogen decline ansd demanded the only treatment that had been proved to be totally

efficacious the demand along with documentation in the 1980s that menopausal estrogen reduce the incidence of osteoprosis.

Hormone replacement therapy is available in many formulations and combination and can be given by various routes also.

Oral Preperation :-

- ❖ HRT using estrogen alone.
- ❖ Cyclic estrogen-progesterone preparation.
- ❖ Continuous Estrogen progesterone preparation.
- ❖ Estrogen-androgen HRT.

Non Oral Preparation :-

- ❖ Vaginal creams and pessaries
- ❖ Percutaneous gel
- ❖ Transdermal patch.

Oral preparation - available are -

A. *Conjugated steroidal estrogens.*

a. ***Estrones***

- ❖ Conjugated equine estrogen.
- ❖ Esterified estrogen.
- ❖ Peperazene estrone sulfate.

b. ***Estradiol Cypiovate***

- ❖ Estradiol Valerate
- ❖ Micronised 17 beta estradiol

c. ***Estriols***

- Estrioal
- Estriol hemisuccinate.

B. *Unconjugated steroid analogues.*

- 17 Ethnyl estradiol
- 17 Ethnyl estradiol 3 methyl ether
- 17 Ethnyl estradiol 3 cyclo pentoether.

C. *Synthetic Estrogen analogues*

- Bengestrol
- Chlorotreanenene.
- Dinestrol.
- Diethylstilboestrol.
- Hexestrol.
- Promethestrol depropriovate.

II. Non Oral Preparations

- Earliest non oral routes of administration used :-
  - Vaginal cream
  - Pessaries
  - Subcutaneous estradiol implant.
- More Recently
  - Percutaneous gel
  - Hormone containing vaginal rings

- Most Recent
  - Transdermal therapeutic system.
  - Only estrogen containing
  - Oestrogen & progesterone

Oral HRT Using Estrogen Only :-

This regimen is most frequently used in patients with surgical menopause , means postmenopausal women who have undergone hysterectomy. In these patients , the addition of progestrone is unnecessary since the need of endometrial protection does not exist.

Daily estrogen are the prefered method of HRT in these cases.

Only estrogen therapy can be given in non-hysterectomised women, with careful monitoring and annual screening endometrial biopsy. Method of therapy - cyclic administration of estrogen (3 weeks on and one week off) has been suggested to reduce the risk of hyperplasia.

Cyclic Estrogen-Progesterone HRT :-

This regimen is frequently used in the post-menopausal patient with intact uterus.

The estrogen correlate the vasomotor disturbance and genitourinary atrophy and presents osteoporosis, progesterone is added exclusively to protect the endometrium from the development of hyperplasia and carcinoma endometrium.

Progesterone that have been clinically assessed for such protection are Norethisterone 5 mg. Medroxy progesterone acetate 10 mg. and dydrogesterone 10mg.

Disadvantage of Progesterone :-

- Vaginal bleeding

Hence long term complaint is poor side effect of progesterone include symptoms similar to premenstrual syndrome. It is also major factor leading to non-compliance.

Continuous estrogen progesterone HRT :-

Since withdrawal bleeding is unacceptable to most patients, combined continuous regimen may improve compliance, this regimen using conjugated estrogen 0.625 mg and medroxy progesterone acetate 2.5 mg and 5 mg.

Only Progesterone HRT :-

Progesterone may be used in perimenopausal HRT when cyclic disturbance predominate and in cases when estrogens are contraindicated progesterone is used as HRT.

Non-Oral Routes :-

Oral estrogen have been shown to be effective in terms of relieving menopausal symptoms (Camp bell and whitehead 1977) and may reduce the risk of ischemic heart disease (Loss et al 1981). However, oral estrogens may cause adverse effect d/t first pass metabolism in liver. To eliminate these adverse

effects , various new routes of hormone administration have been developed , which means estrogen and progesterone can be given non-orally.

The earliest non-oral routes of estrogen administration are vaginal cream , pessaries , subcutaneous estradiol implant, more receutly, percutaneous skin gel and hormone containing vaginal ring have been developed. The transdermal therapeutic patches are the most recent development and have advantages over the older , delivery systems.

1. Vaginal Cream :

In the late 1970s, it was realized that a significant amount of estrogen could be absorbed through the vaginal epithelium (Bigg et al, Schiff et al 1977). the efficiency with which estrogen absorbed are demonstrated by whithead et al 1978. It estrogen are given in adequate doses vaginally, the to will cause endometrial proliferation, so in these patients, cyclic progesterone is advisable. Fink et al (1985) have suggested the use of vaginal oestrial as a safe and effective alternative to CEE cream. Daily dose of 0.5mg improve both vasomotor and urogenital symptoms continuous 3 months administration caused proliferative changes in endometrium but not hyperplasia.

2. Vaginal Ring/ Pessaries :

In 1970s, filicome ring 3 impregnated initially with progesterone (Mishell et al 1970) and subsequently a

combination of oestradiol and d-norgestrol (Mishell et al 1978) were shown to be effective method of contraception various attempts have been made at using them in post-menopausal female , and although effective, they are not particularly popular among patient.

Estradiol rings release 8 mg estradiol/24 hours at a constant rate. The ring is easy to insert and remove as it is soft and flexible. Each ring is to be used continuously for 90 days and is well tolerated , giving significant relief from vaginal dryness, itching, dyspareunia and dysuria.

3. Subcutaneous oestradiol implants :-

This mode of therapy is not new, being initialy pioneered by Greenblatt in the USA (Greenblatt and Suran 1949), Most recently there use has been encouraged in UK (Studd 1976). Small oestradiol pellets , of various doses , are inserted into the subcuteneous fat of the anterior abdominal wall using a trocar.

The implants consist of biodegradable crystalline steroid pellets in permeable silastic rods. They are cylindrical in shape and vary from 3-6 mm in length and 2.2-4.5 mm in diameter depending upon the dose. The implant contain 17-beta estradiol (25/50/100 mg) in a cholesterol base. Implantation is easy and is performed under local anaesthesia with specially designed trocar and cannula, into the subcutaneous fat of

either abdominal wall 5 cm. above and parallel to the inguinal ligament or over the buttocks taking care to avoid the sheath, .muscle or any scar tissue, the oestradiol implants usually last for upto 6 month peak levels of oestradiol and oestrogen are achieved 1-2 month after implantation and begins to decline there after.

In women with intact uterus , cyclic progesterone therapy is indicated , hence hormone implants are prefered for HRT in women who have undergone a hysteractomy and may be inserted at the time of surgery.

Complication of Implants therapy are rare , bleeding at insertion site usually , responds to pressure. tachyphylaxis may be induced by frequent reinplantation and can be avoided by pretreatment counseling. Oestradiol implants appear to be effective in preventing post-menopausal bone loss (Magos and studd 1990 Maesseu 1993).

More Recently :-

1. Percutaneous gel - Oestradiol gel :-

17 Beta - Oestradiol , when applied to the skin in a hydroalcohalic base , can easly penetrate the outer stratum corneum. Some passes into the microvasculature beneath the epidermis and then into the systemic circulation, part of the estradiol is retained in the stratum corneum , to be absorbed

into the circulation over 24 hours , untill the next application of gel.

About 10% of total dose of oestradiol is absorbed once the alcohal has evaporated from skin , no further absorption can take place. In place, where temperature are higher , evaporation of alcohal is quicker and less amount of drug is absorbed.

Most Recently :-

Transdermal device first introduced in July 19, 1983. It is based on the theory that oestrones could be produced in oopherectomized mice by the application of oestrogen cream on the skin (1920 sand1930s).

Transdermal delivery of estradiol by a skin patch developed by Schenkel et al (1985) is now well established. Transdermal administration of estradiol appear to be at least as effective as oral Conjugated estrogen therapy on most of the end point which have been evaluated but allows a lower dose to be used. Thus avoiding some of the metabolic adverse effect experienced with oral treatment.

Structure of System

The transdermaltherapeutic system is a cutaneous device which delivers estradiol into systemic circulation via the stratum corneum at a constant rate upto 4 days.

It is thin adhesive patch , consisting of a drug reservoir where estradiol is held in ethanol solution between an occlusive backing layer and a rate limiting microporous membrane.

Three sizes of estradiol patches currently available as Estraderm TTS-25, Estraderm TTS-50 and Estraderm TTS-100 contain 2,4, and 8 mg of drug,. respectively and desired to release estradiol at a rate of 0.21 ug/cm^2/hour. Correspondingly to four days. These maintain blood level of 25 pg/ml, 40 pg/ml and 75 pg/ml respectively with small fluctuations.

Site of application :

Hairless skin of buttocks is most suitable site of application of patch, other sites are abdomen , lateral thorex, upper arm and breaset.

Proven Beneficial Effects of Estrogen Therapy on Menopausal Symptoms -

The beneficial effects of estrogen therapy on menopausal symptoms are certainly better known and understood than those of many drugs.

1. The Hot flushes are appearing the most typical and most sensitive indicator of the effectiveness of estrogen.

Hot flushes and profuse sweating are quickly and significantly reduces by estrogen treatment (Greenblatt et al 1950 ; lauritzen 1973, Utian 1975 , Coope 1976).

2. Atrophic cystitis and urethritis with corresponding symptoms can certainly be ameliorated by estrogen medication as shown by urinary cytology and disappearance of complaints (Hoffmann 1950 a,b, Lauritzen 1968, Jonsson 1973 ,Smith 1977).

3. Estrogen also improve the readiness for social contact and Psychic allertness in aged women (Caldwell 1952, Caidwell and wetson 1954 , Dueker 1957 , Evans and Marmorston 1963).

4. Estrogen medication also abolishes dizziness and tingling sensation and the concomittant rise of blood pressure which occurs with hot flushes (Lauritzen and Velizese 1961).

5. Vulval atrophy and vulvitis based on atrophy are consistently and safely improved by estrogen administration either locally or parentrally (Lauritzen 1970, Rauramo 1976).

6. Estriol , Ethinyl estradiol and estradiol valvate have been reported to reduce first and even second degree stress

incontinance (Lambillion 1971 , Waiiner and Scost 1971, Caine and Raz 1973, Dexelmuller 1974).

7. The beneficial effect of estrogen on dermal thickness, skin appearance, wrinkles , elasticity and blood perfusion have been studied by Aertgeerts (1972).

8. The atrophic changes which occurs in the skin following oophrectomy can be prevailed by and even reversed by administration of estrogen (Rauramo and Punnonen 1973).

9. A consistant and favourable effects is also obtained by local and parentral estrogen administration in atrophic changs when painful intercourse is the problem (Joswig prieve et al 1973, Lauritzen and Muweller 1977).

10. Estriol increases alertness and attention and there is also improvement of memory (Vanhulle and Drumol 1976).

11. Estrogen replacement therapy is necessary for patients of premature menopause as it helps to reduce cardiovascular and cerebrovascualr disease mortality (Cust & White head 1980).

12. Prospective cohort studies have also shown beneficial effects of HRT in reducing the risk of non spinal fracture

and this was marked in women who began therapy within five year of the menopause and it was unaffected by age or concomitant progestin therapy (Canlay JA,Seeley D.G. , Ensured K, Black D- 1995).

13. Psychological symptom of a wide variety including fatigue,irritability tension , anxiety , mood fluctuations, Headache, insomnia, altered libido etc. are extremely , in post menopausal women, (Mittal S. 1996).

14. A four years randomized study from the university of Taxes showed for the first time on the additive effect of intermittent cyclical etidronate and HRT on the bone mineral density in both vertebral and the hip (Jha U.P. 1997).

Dispite the proven efficacy of the oral route for oestrogen replacement dose related adverse effects are a major drawback 60-90% of an oral estrogen dose is converted into estrone , in the liver ,which is pharmacologically inactive substance.

These substance causes harmful effects on body so the member of non oral forms of estrogen delivery, which avoid first pass met+abolism have been found to be effective in treating menopausal symptoms, but precise control of dosage is difficult with these method.

Recently , a transdermal preparation which delivers estradiol at a constant rate has become available , various studies have also proven the beneficial effects of transdermal route of estrogen as hormone replacement therapy.

In the initial prospective study of the efficacy of the transdermal therapeutic system in post menopausal women. laufer and coworkers (1983) showed that transdermal estradiol delivered from a patch, significantly reduces the incidence of hot flushes, they also reported beneficial effects on vaginal cytology.

Padwick and colleagues (1985) used a graphic rating scale to compare menopause symptoms score before and during the treatment cycles in 12-menopausal women.

MATERIAL AND METHODS

MATERIAL AND METHODS

The present study was carried out in Department of Obstetrics and Gynaecology, M.L.B. Medcial College , Jhansi. The patients were selected from the gynae OPD.

Total 50 post menopausal females with amenorrhoea more than 6 months, or panhysterectomy at lest one month back with one or other climectoric symptoms, were selected for study.

Selection of Patient :-

1. ***Souce*** :✶ Patients are selected from - OPD
   - Gynae ward
   - ✶ Natural menopause - Age above 40 yrs.
   - ✶ Artificial menopause - Hysterectomy with or without oopherectomy

2. ***Criteria***
   a. Presenting complain
   - ❖ Hot flushes
   - ❖ Night Sweating
   - ❖ Insomnia
   - ❖ Dry Vagina
   - ❖ Dyspareunia
   - ❖ Palpitation

- Burning Micturition
- Vaginal discharge
- Frequency and Urgency of urine
- Jotter syndrome
- Oligomenorrhoea
- Bone pains
- Spontaneous fracture
- Dry Skin
- Dry hair
- Dry mouth.

b. *History of patient*

Name, Age, parity, caste, Socio-economic Status, place of residence, occupation

- Age of menopause
- Menstrual History
- Obstetrical History
- Personal History
  - Smoking
  - Alcohol
  - H/O past surgery
  - Race
- Past History
  - Tuberculosis
  - Hypertension
  - Ischemic Heart disease

- Diabetes Mellitus
- Malignancy

❖ Family History

- Menopause
- Cardiovascular disease
- Malignancy
- Diabetes mellitus

❖ Drug History

b. Clinical Examination

General Examination :

General condition, weight, Blood pressure, pulse rate, Respiratory rate , Body temperature, pallor, cynosis, Jaundice odema lymphadenopathy.

❖ Chest Examination

❖ Cardiovascular system

- Any evidence of
- Coronary artery disease
- Hypertension
- thromboembolic phenomenon.

❖ Central Nervous System

- Irritability.
- Loss of memory.
- Any psychological symptom.

Abdomin :

- Any lump
- Scar mark
- Hepatosplenomegaly

Breast Examination for

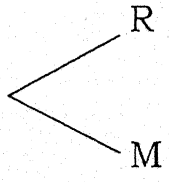
- Lump
- Discharge
- Tenderness

Perspeculum and pervaginal Examination

- Condition of vaginal and vaginal secretion.
- Any pathology of cervix
- Size and position of uterus and adenexa.

C. *Investigations*

Hemogram

- Hb% , TLC , DLC , ESR
- Urine 

- Blood sugar
- Electro cardiogram

Lipid Profile

- Total serum cholesterol
- Serum triglyceride
- High Density Lipoprotein

- Low Density Lipoprotein.

Liver function test

- Serum bilirubin
- SGOT , SGPT

Method of Collection of Blood Control

5 ml of blood was withdrawn from antecubital vein of the female in recumbent posture with all aseptic precautions,

- After 12-14 hour of fasting.
- After 10 minutes of supine rest.
- Without venous stasis.

After withdrawal blood was allowed to settle down for half an hour and then centrifuged and serum was preserved with standard precautions.

Period of Collection of Blood Sampel -

1. Basal Sample (before HRT).
2. After 2 months of HRT.
3. After 6 months of HRT.

Estimation of Lipid Factors

Various lipid factors , serum total cholesterol (STC), serum triglyceride (STG), high density lipoprotein (HDL) were estimated by diagnostic kits while low density lipoprotein (LDL) and very low density lipoprotein (VLDL) and HDL/LDL

ratio were derived from values of above mentioned lipid by standard formulae.

1. Method of Estimation of Various Lipid Factors -

Serum total cholesterol (STC) was estimated by commercial kit supplied by Ethnor. The basic principle is that cholesterol reacts with kits solution of ferric perchlorate, ethyl acetate and sulphuric acid and gives levender coloured complex which is measured colorimetrically.

2. Estimation of Serum Triglyceride (STG) -

Serum triglyceride was estimated by acetyle acetone method. Principle behind this is that triglycerides are determined by measuring glycerol after its liberation from fatty acids by saponification glycerol is oxidised by sodium metaperiodate to formaldehyde which is directly proportional to the amount of triglycerides.

3. Estimation of High Density Lipoproteins (HDL) -

HDL were estimated by utilising commercial kit supplied by Ethnor. Basic principle is that the HDL cholesterol fraction is separated by using a precipitating reagent.The precipitants contains chylomicrons, VLDL, LDL, which are removed by centrifugation . The supernatants contain HDL cholesterol which is estimated by HDL-C colour reagent which gives purple coloured complex intensity of colour developed is

proportional to the concentration of HDL cholesterol in the specimen under test.

4. **Estimation of very Low Density Lipoprotein (VLDL) -**

VLDL was estimated by the formula given by Friedwald et al (1972).This formula is valid upto STG values to less than 400 mg%.

VLDl(Mg/dl) = STG/5.

5. **Estimation of Low Density Lipoprotein (LDL) -**

LDL was estimated by using fredrickson DA (1972) formula :

LDL(mg/dl) = STC + (STG/5 + HDL)

= STC - (VLDL + HDL)

Estimation of ratio LDL/HDL was done by values of LDL and HDL.

Vaginal Cytology - For exfoliative cytology :- Equipments Cusco's speculum, cotton swab , Ayre's spatula, container with spirit & ether (1:1) These would be done before the commencement of therapy. Investigation repeated after 2 months and 6 months and clinical examination repeated monthly.

Exclusion of Patients :

Following patients were excluded from study group such as

- Patients with undiagnosed vaginal bleeding, genital neoplasm, carcinoma breast or history of carcinoma breast in family.
- Patients who had any major complication in post operative period.
- Patient with cardiovascular disease , hypertension diabetes mellitus , H/o jaundice , and thromboembolic phenomenon were not included in this study.

Selection of patients :-

The post menopausal patients were selected from the patient attending the out patients department of obstetrics and Gynaecology of M.L.B. Medical College , Jhansi.

A seperate record of such patients were kept of register , maintained for this very purpose only. This procedure were adopted till the number of the postmenopausal patients attained the number fifty. Date wise serial number was attained to the cases. These fifty patients were divided into five groups. As such each group were comprised of ten post menopausal cases amongst these five groups one will be treated as control group. While remaining four groups will receive the drugs.

Viz. 1. Premarin 2. Evalon 3. Ovaral-L 4. E_2 gel

The selection of cases for the various drugs were made on the basis of systemic random sampling. Since there are five

groups and total number of the patients is fifty , hence 50/5 = 10. Now from random number table, any random number ≤10, Since there are five groups , were chosen , and then every next fifth patients were given drug number 1, and then starting from next number to chosen random number were given drug 2, and so on for 3rd , 4th and conrol group , till the list of the patients gets exhausted.

Mode of Administration of drugs :

Oral

a. Tab premarin 0-625 mg/day given in cyclical manner (3 weeks on with one week off)

b. Tab evalon 1 mg/day given in cyclic manner.
(3 week on with one week off).

c. Tab ovral-L levonargestrel 0.15 mg + ethinyl oestradiol 0.03 mg.
One tab/day given in cyclic manner.
(3 weeks on with one week off).

d. Transdermal Estrogen
   - E2 gel (17 beta strediol 0.06% w/w).
   - 2.5 gm gel containing 1.5 mg. of estrogen apply twice a week at forarm , arm and shoulder.
   - Madroxy progesteral 10 mg/dy. given in last 10 days (each cycle inpatients having intact uterus).

e. Control group : Oral calcium tablet given 1000 mg/day.

Clinical examination was done monthly for 6 months and routine investigation after 2 months and 6 months.

Enquiry would be made upon :-

a. Control of symptoms.

b. Withdrawal bleeding.

In non hysterectomized patient - whether withdrawal bleeding has occurred or not.

c. Health education advice.

- Regular self breast examination.
- Diet
- Exercise
- Stress management
- Reduction in tabacco and alcohal consumption.

d. Control or weight gain

e. Blood pressure.

Breast examination

f. ***Investigation if indicated***

- Pelvic ultrasound
- Cervical biopsy
- Serum cholesterol
- Endomaterial biopsy
- Mamography.

OBSERVATIONS

OBSERVATIONS

In the present study the ***effect of different type of HRT on Serum lipid lipoprotein , Clinical Symptoms and Vaginal Cytology.*** The study was conducted in the department of Obstetrics & Gynaecology , M.L.B., Medical College Jhansi. The Patients selected from Gynae OPD.

The total 50 patients where included in the study and they were divided into bio groups. i.e. :

1. Premarin Group.
2. Evalon Group.
3. E_2 Gel Group.
4. Ovral-L Group.
5. Control Group.

A pretreatment sampling was withdrawn and subsequent samples were taken after 2 months and 6 months of therapy. The effect on serum lipoprotein levels was studied by comparing the basal levels with subsequent levels.

The evaluation in clinical symptoms are depends on patients feelings and statements after 2 months and 6 months therapy and compare with control group.

Vaginal cytology taken pretreatment and after 2 months and 6 months of therapy. Evaluations shown by tables and

compared with control group. The serum lipoprotein, Vaginal cytology and clinical symptom observed result are mentioned in the various following tables -

Table - I : Distribution of Cases According to Age with HRT Group.

Sl. No.	Age. yrs.	Premarin		Evalon		E_2 Gel		Ovral-L		Control Group	
		No. (10)	%	No. (10)	%	No. (10)	%	No. (10)	%	No. (10)	%
1.	40-45	3	30	3	30	3	30	1	10	1	10
2.	46-50	4	40	3	30	5	50	8	80	7	70
3.	51-55	1	10	3	30	2	20	1	10	2	20
4.	56-60	1	10	1	10	Nil	-	Nil	-	Nil	-
5.	61-65	Nil	-	Nil	-	Nil	-	Nil	-	Nil	-
6.	66-70	1	10	Nil	-	Nil	-	Nil	-	Nil	-

Age of patient selected for study was 40-70 years. Maximum No. of patients were between 46-50 years in all 5 groups such as 40% in Premarin , 30% in Evalon , 50% in E_2 gel , 80% in Ovral-L and 70% in Control group. Only 10% in this study was between 66-70 years age which was in Premarin. No patients under 61-65 year of age. In 40-45 year age there was 30% in Premarin , 30% in Evalon , 30% in E_2 gel , 10% in Ovarl-L and 10% in control group. In 51-55 year of age 10% cases in premarin , 10% in Evalon. In 56-60 year of age 10% cases in premarin and 10% cases in Evalon.

Table - II : Distribution of Cases According to Parity with HRT Group.

Sl. No.	Parity	Premarin		Evalon		E_2 Gel		Ovral-L		Control Group	
		No. (10)	%	No. (10)	%	No. (10)	%	No. (10)	%	No. (10)	%
1.	Nullipara	-	-	-	-	-	-	-	-	-	-
2.	Primipara	-	-	-	-	-	-	-	-	-	-
3.	Multipara	3	30	6	60	5	50	3	30	7	70
4.	Grand Multipara	7	70	4	40	5	50	7	70	3	30

The above table shown distribution of cases according to parity of patients. No cases presented with nullipara and primipara. The Grand multipara presented with slightly higher percentage (52%), In which 70% cases in premarin , 40% cases in evalon , 50% cases in E_2 gel , 72% cases in Ovral-L and 30% cases in Control group. Multipara women presented with 48% of cases in which 30% in premarin , 60% in evalon , 50% in E_2 gel, 30 % in Ovral-L and 70% in Control group.

Table - III : Distribution of Cases According to Duration of Menopause from onset.

Sl. No.	Duration of Menopause	Premarin		Evalon		E_2 Gel		Ovral-L		Control Group	
		No. (10)	%	No. (10)	%	No. (10)	%	No. (10)	%	No. (10)	%
1.	0 - 5 yrs.	7	70	9	90	10	100	9	90	10	100
2.	6 - 10 yrs.	2	20	1	10	-	-	1	10	-	-
3.	10-15 yrs.	-	-	-	-	-	-	-	-	-	-
4.	16-20 yrs.	1	10	-	-	-	-	-	-	-	-

The above table shown maximum no. of cases presented with 0-5 years. of menopause amongst them 70% premarin , 90% cases in evalon , 100% cases in E_2 gel , 90% cases in Ovaral-L and 100% cases in Control group. In 6-10 years of menopause In which 20% cases in premarin , 10% cases in evalon , 10% cases in Ovral-L. no cases presented with 11-15 years. of menopause in our study. In 16-20 years. of menopause, only one case presented which was belongs to premarin group.

Table - IV : Effect of HRT on Serum Lipid after 2 months and 6 months of therapy (mean ± SD, mg/dl) and statistical significance

S. Lipids	Drug	Before therapy (A) (mean ± SD)	After 2 months (B) (mean ± SD)	After 6 months (C) (mean ± SD)	Statistical Significance		
					A : B	A : C	B : C
STC	Premarin	216 ± 26.75	213.6 ± 24.42	203.5 ± 20.41	t = 3.20 P<0.05	t = 5.83 P<0.01	t = 6.02 P<0.01
STG	Premarin	127 ± 21.63	129.6 ± 20.09	134.1 ± 30.17	t = 2.74 P<0.05	t = 5.36 P<0.01	t = 5.78 P<0.01
HDL	Premarin	41.1 ± 5.78	42 ± 5.29	45.5 ± 5.25	t = 2.44 P<0.05	t = 8.77 P<0.01	t = 10.00 P<0.01
LDL	Premarin	150.8 ± 18.10	145.6 ± 19.67	131.1 ± 14.05	t = 7.37 P<0.01	t=10.70 P<0.01	t = 9.48 P<0.01

The above table shown mean changes in serum lipid lipoprotein (STC, STG,HDL, LDL). A ratio of pretreatment to after 2 months of therapy (A : B) , A ratio of pretreatment after 6 months of therapy (A : C) and A ratio of after 2 months to 6 months of therapy (B : C) as below.

Statistical significance :

Serum total cholesterol (STC)

A : B , t = 3.20 significant at P < 0.05

A : C , t = 5.83 significant at P < 0.01

B : C , t = 6.02 significant at P < 0.01

Serum Triglyceride (STG)

A : B , $t = 2.74$ significant at $P < 0.05$

A : C , $t = 5.36$ significant at $P < 0.01$

B : C , $t = 5.78$ significant at $P < 0.01$

High Density Lipoprotein (HDL)

A : B , $t = 2.44$ significant at $P < 0.05$

A : C , $t = 8.77$ significant at $P < 0.01$

B : C , $t = 10.00$ significant at $P < 0.01$

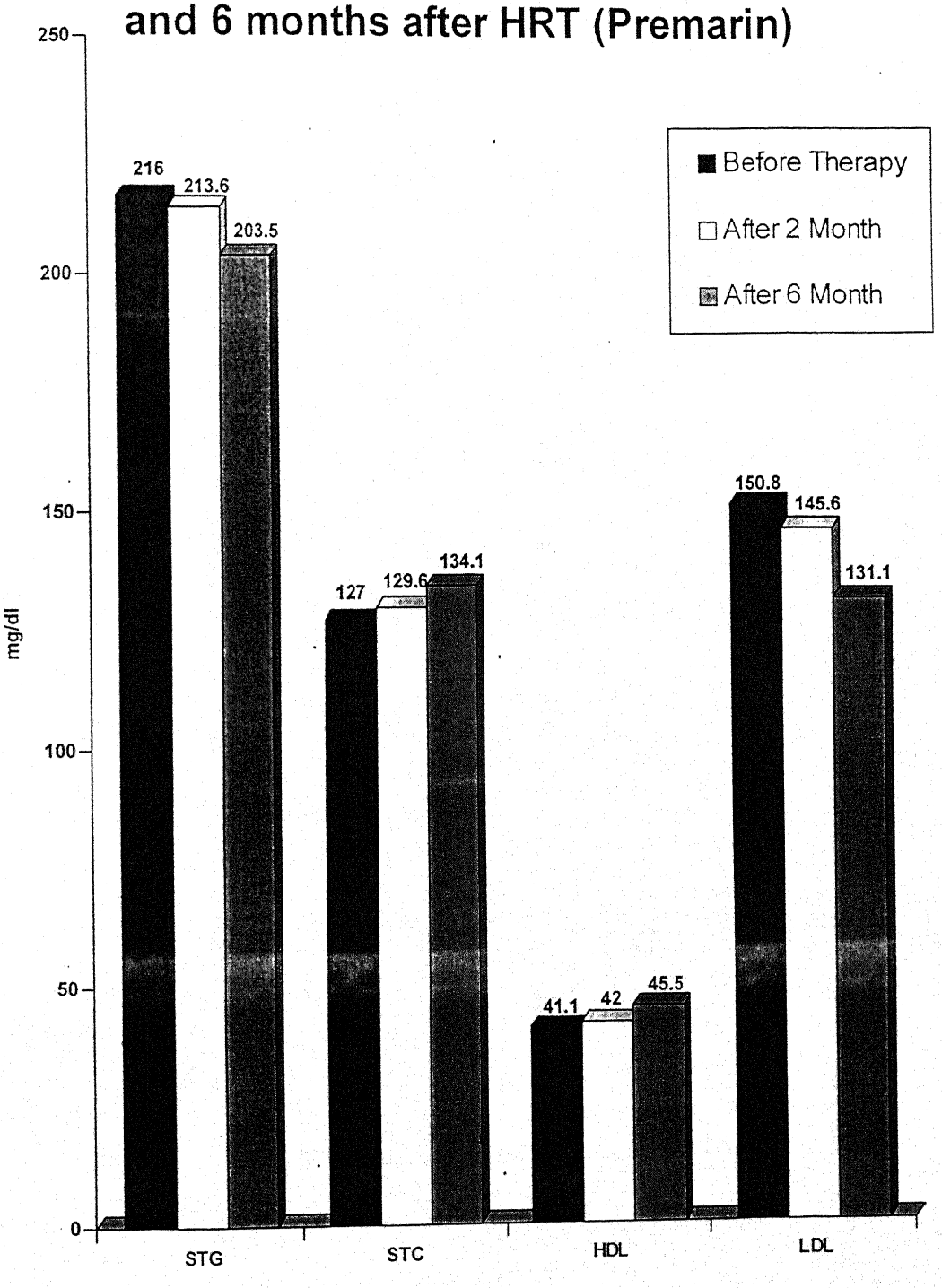
Low Density Lipoprotein (LDL)

A : B , $t = 7.37$ significant at $P < 0.01$

A : C , $t = 10.70$ significant at $P < 0.01$

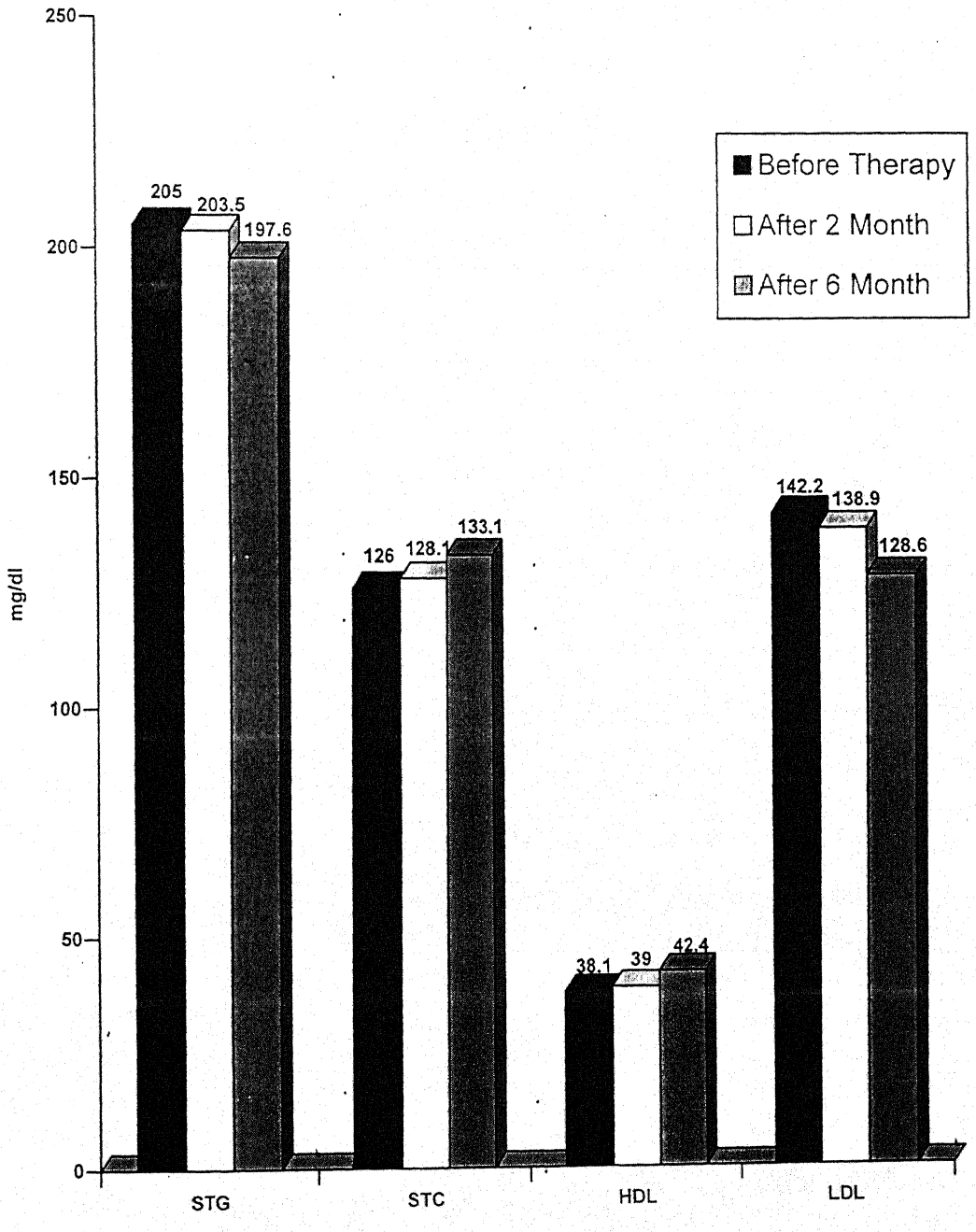
B : C , $t = 9.48$ significant at $P < 0.01$

Bar Diagram :Mean Serum Lipid Lipoproteins Basal and after 2 months and 6 months after HRT (Premarin)



Serum Lipid Lipoproteins

Bar Diagram :Mean Serum Lipid Lipoproteins Basal and after 2 months and 6 months after HRT (Evalon)



Serum Lipid Lipoproteins

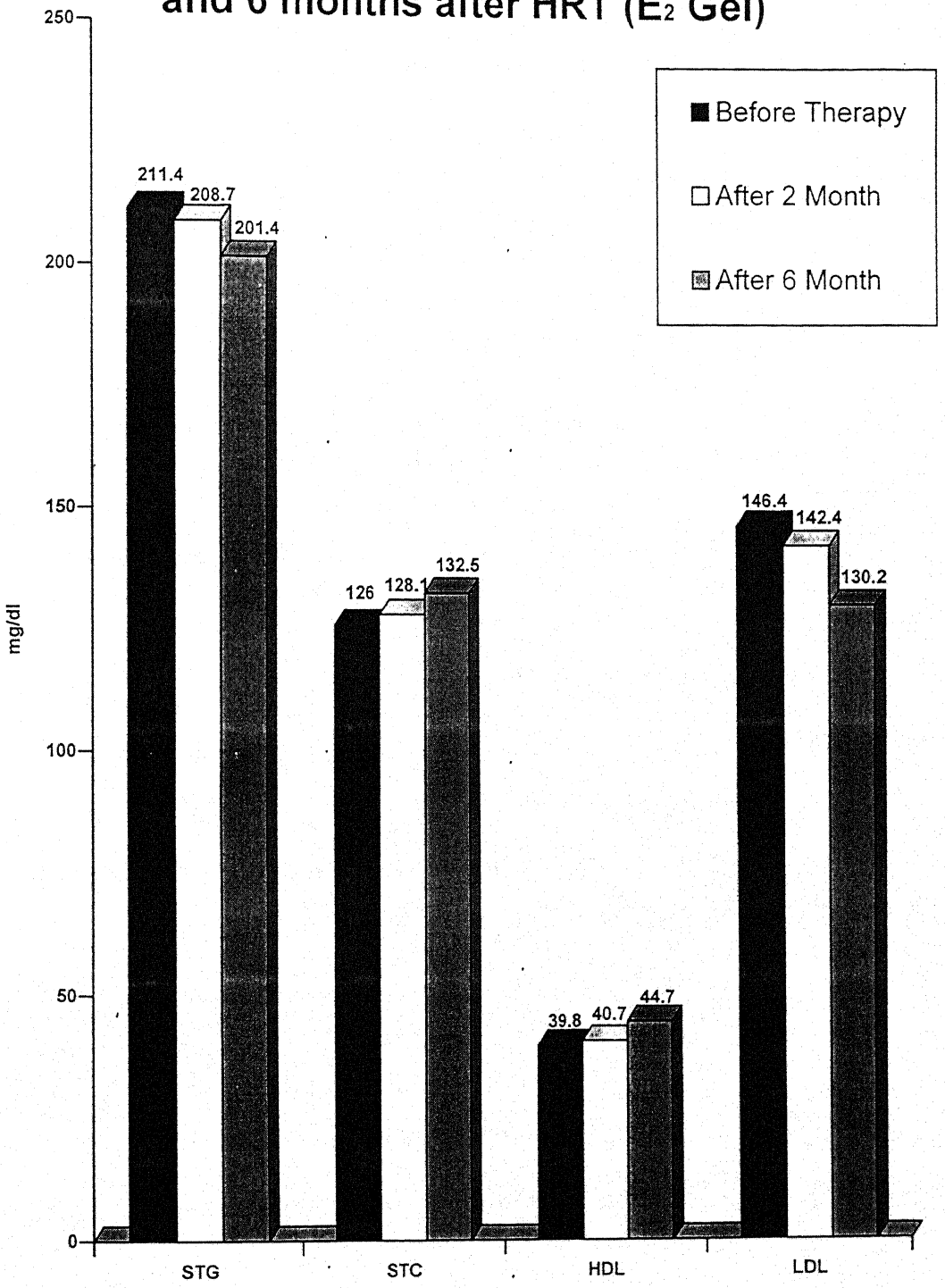
Table - VI : Effect of HRT on Serum Lipid after 2 months and 6 months of therapy (mean ± SD, mg/dl) and statistical significance

S. Lipids	Drug	Before therapy (A) (mean ± SD)	After 2 months (B) (mean ± SD)	After 6 months (C) (mean ± SD)	Statistical Significance		
					A : B	A : C	B : C
STC	E2 Gel	211.4 ± 21.94	208.7 ± 18.30	201.4 ± 15.00	t = 2.63 P<0.05	t = 4.37 P<0.01	t = 6.55 P<0.01
STG	E2 Gel	126 ± 23.19	128.1 ± 23.09	132.5 ± 17.66	t = 2.36 P<0.05	t = 2.44 P<0.05	t = 2.37 P<0.05
HDL	E2 Gel	39.8 ± 5.63	40.7 ± 5.15	44.7 ± 6.44	t = 2.87 P<0.05	t = 6.56 P<0.01	t = 9.72 P<0.01
LDL	E2 Gel	146.4 ± 13.96	142.4 ± 10.43	130.2 ± 7.71	t = 5.30 P<0.01	t = 7.72 P<0.01	t = 8.00 P<0.01

The above table shown effect of E2 gel (17 beta oestradiol) therapy on Serum Lipid Lipoproteins mean changes, (STC, STG,HDL, LDL) from before therapy to after 2 month and 6 month of therapy and statistical significance. A ratio of pretreatment to after 2 months of therapy (A : B) , A ratio of pretreatment after 6 months of therapy (A : C) and A ratio of after two months to 6 months of therapy (B : C) also shown.

Serum triglyceride not shown gradual significant changed after 2 months and after 6 months of therapy. STC ,HDL and LDL shown gradual significant changes toward its expected direction of estrogen therapy.

Bar Diagram :Mean Serum Lipid Lipoproteins Basal and after 2 months and 6 months after HRT (E_2 Gel)



Serum Lipid Lipoproteins

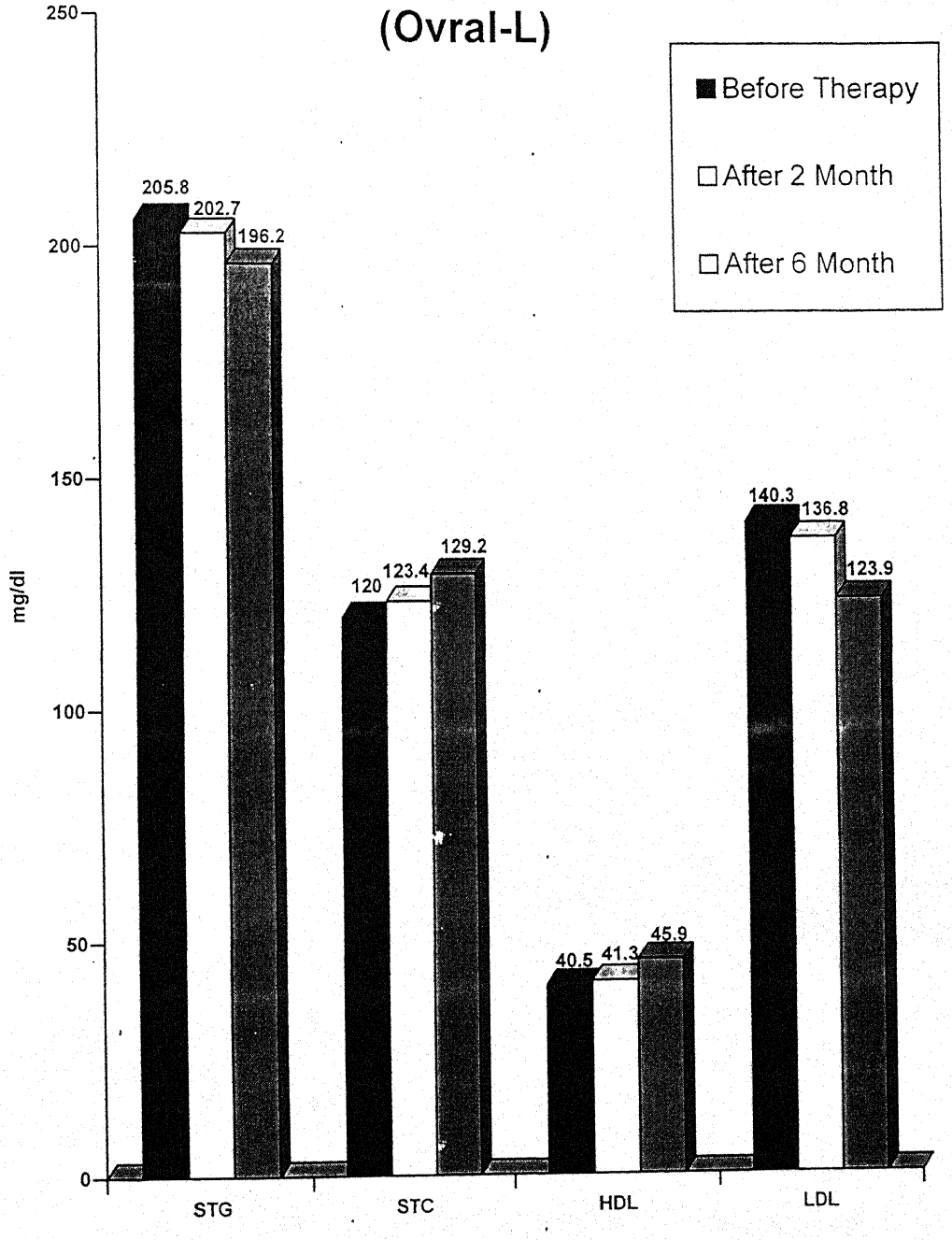
Table-VII : Effect of HRT on Serum Lipid after 2 months and 6 months of therapy (mean ± SD, mg/dl) and statistical significance

S. Lipids	Drug	Before therapy (A) (mean ± SD)	After 2 months (B) (mean ± SD)	After 6 months (C) (mean ± SD)	Statistical Significance		
					A : B	A : C	B : C
STC	Ovral-L	205.8 ± 23.10	202.7 ± 19.02	195.2 ± 14.35	t = 3.09 P<0.05	t = 5.26 P<0.01	t = 6.44 P<0.01
STG	Ovral-L	120 ± 21.08	123.4 ± 19.01	129.2 ± 16.84	t = 3.20 P<0.05	t = 5.43 P<0.01	t = 10.27 P<0.01
HDL	Ovral-L	40.5 ± 3.71	41.3 ± 4.50	45.9 ± 5.70	t = 2.75 P<0.05	t =11.93 P<0.01	t = 15.10 P<0.01
LDL	Ovral-L	140.3 ± 17.39	136.8 ± 13.63	123.9 ± 10.47	t = 4.34 P<0.01	t =11.97 P<0.01	t = 10.27 P<0.01

The above table shown effect of Ovral-L on Serum Lipid Lipoproteins mean changes, (STC, STG, HDL, LDL) from before therapy to after 2 month and 6 month of therapy and statistical significance. A ratio of pretreatment to after 2 months of therapy (A : B) , A ratio of pretreatment after 6 months of therapy (A : C) and A ratio of after two months to 6 months of therapy (B : C) also shown.

There are gradual statistical significant changed shown towards its expected side in all four entities (STC, STG, HDL, LDL).

Bar Diagram :Mean Serum Lipid Lipoproteins Basal and after 2 months and 6 months after HRT (Ovral-L)



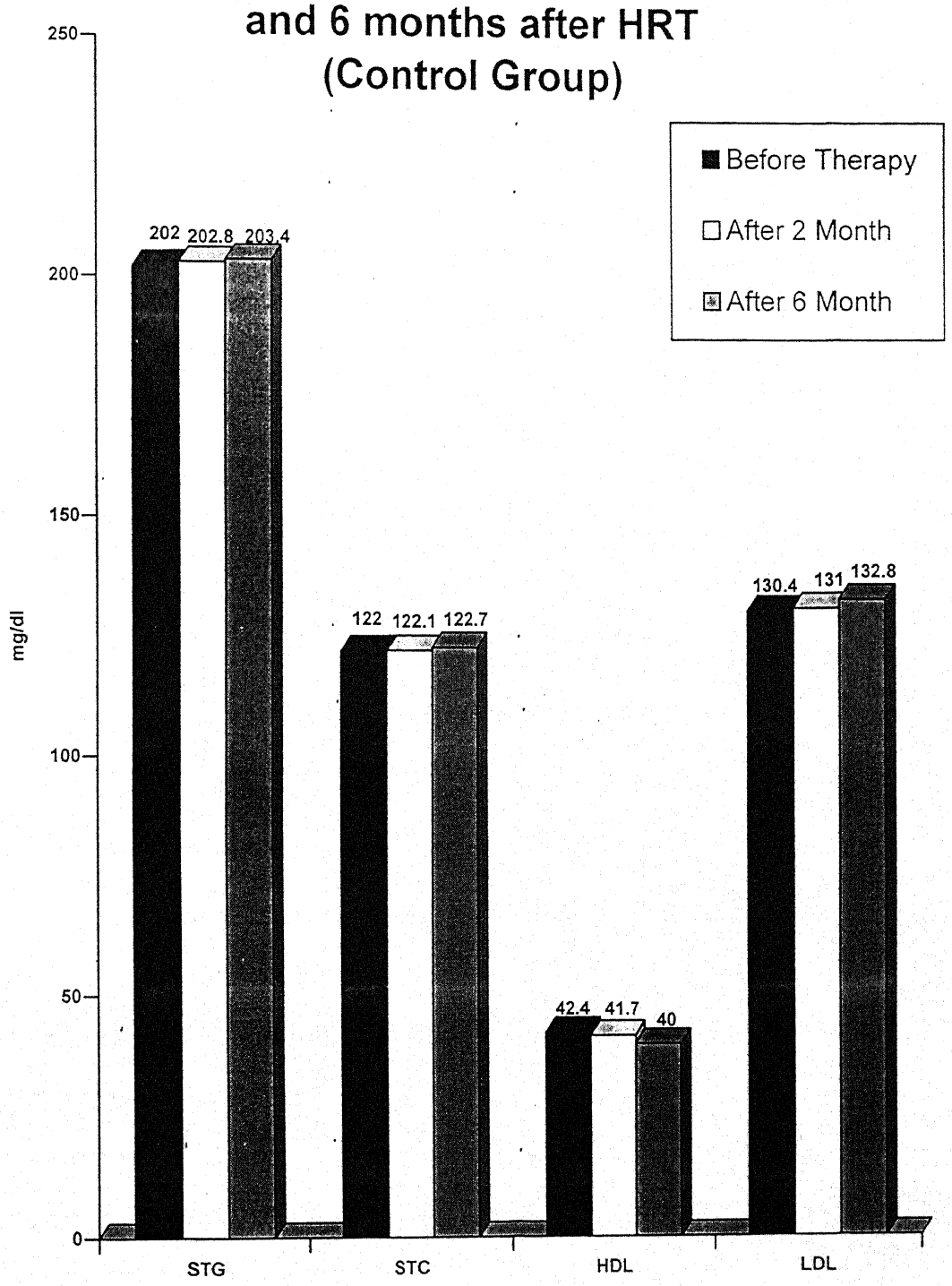
Serum Lipid Lipoproteins

Table-VIII : Effect of HRT on Serum Lipid after 2 months and 6 months of therapy (mean ± SD, mg/dl) and statistical significance

S. Lipids	Control Group	Before therapy (A) (mean ± SD)	After 2 months (B) (mean ± SD)	After 6 months (C) (mean ± SD)	Statistical Significance		
					A : B	A : C	B : C
STC	Plecebo	202 ± 15.42	202.8 ± 13.00	203.4 ± 15.94	t = 2.09 P>0.05	t = 2.20 P>0.05	t = 2.97 P<0.05
STG	Plecebo	122 ± 30.11	122.1 ± 28.73	122.7 ± 27.34	t = 1.00 P>0.05	t = 1.25 P>0.05	t = 2.17 P>0.05
HDL	Plecebo	42.4 ± 4.47	41.7 ± 5.00	40.0 ± 4.55	t = 1.97 P>0.05	t = 3.20 P<0.05	t = 2.07 P>0.05
LDL	Plecebo	130.4 ±10.66	131.0 ± 7.81	132.8 ± 11.48	t=2.20 P>0.05	t = 4.5 P<0.01	t=3.20 P<0.05

The above table shown changes in Mean Lipid Lipoproteins (STC, STG,HDL, LDL) after 2 months and 6 months of observation. There are statistical significant , come in LDL after 6 months of observation (t=4.5 significant at $p<0.01$). In other group of serum lipid lipoproteins there are increase or decrease but no statistical significant at $P<0.01$.

Bar Diagram :Mean Serum Lipid Lipoproteins Basal and after 2 months and 6 months after HRT (Control Group)



Serum Lipid Lipoproteins

Table - IX : Distribution of Cases According to Clinical Symptoms.

Clinical Symptoms	Premarin		Evalon		E2 Gel		Ovaral-L		Control Group	
	No.	%	No.	%	No.	%	No.	%	No.	%
Vaso./Uro	1	10	-	-	1	10	-	-	3	30
Vaso./Psycho	4	40	5	50	3	30	4	40	4	40
Uro./Psycho.	2	20	2	20	4	40	3	30	3	30
Psycho./Late Conse.	2	20	1	10	-	-	-	-	-	-
Vaso./Uro/ Psycho.	1	10	2	20	2	20	3	30	-	-
Total	10	100	10	100	10	100	10	100	10	100

Note :- No case with the Combination of Symptoms Viz. Vaso./Late, Uro/Late, Uro./ Psycho/ Late Conse., Vaso/Uro/Psycho./ Late

This table shown distribution of cases according to clinical manifestations in menopausal women maximum number of cases where presented with vasomotor/psycholgical symptoms (40%) in which 40% cases in premarin , 50% cases in evalon 30% cases in E_2 gel , 40% cases in ovral-L and 40% cases in control group. Next common group of symptoms presented with urogenital/psychological symptoms (30%). In which 20% cases in premarin, 20% cases in evalon 40%, cases in E_2 gel, 30% cases in ovarall L and 40% cases in

control group. Vasomotor/Urogenital symptoms presented with 10% in premarin, 10% in E_2 gel and 30% in control group. Let consequences/psychological symptoms presented with 20% in premarin and 10% in Evalon. More than 2 grup of symptoms presented with vasomotor/Urogenital/Psychological in which 10% in premarin , 20% cases in Evalon , 20% cases in E_2 gel and 30% cases in ovral-L.

Table - X : Distribution of Cases According to Symptom Relief after 2 months and 6 months of Hormone Replacement Therapy.

Symptoms Relief	Premarin		Evalon		E2 Gel		Ovral-L		Control Group	
	After 2 months	After 6 months	After 2 months	After 6 months	After 2 months	After 6 months	After 2 months	After 6 months	After 2 months	After 6 months
No Change	-	-	-	-	-	-	-	-	7	6
Some Extent	5	0	5	0	4	0	9	0	3	4
Significant	5	1	5	1	6	0	1	2	0	0
Complete Abolition	0	9	0	9	0	10	0	8	0	0
Total	10	10	10	10	10	10	10	10	10	10

This table shown in relief of symptoms according to patients statement after 2 months of therapy in premarin 50% cases symptoms relief some extent and 50% cases significant relief. In Evalon 50% cases having symptoms relief some extent and 50% cases significant relief. In E_2 gel 40% cases shown some symptom relief and 60% shown significant relief in symptoms. In ovaral-L 90% cases represented some extent symptoms relief and 10% shown significant relief in symptom. Control group (taken calcium in plecebo therapy) shown 30% symptoms relief some extent and 70% shown no changed in presenting symptoms. After 6 months of HRT, in premarin 90% cases presented complete abolition in symptoms and 10% cases represented significant relief. In Evalon 90% cases represented complete abolition in symptoms in 10% cases represented significant relief in symptomps. In E_2gel 100% cases represented complete abolition in symptoms. In ovaral-L 80% cases represented complete abolition in symptoms and 20% cases represented significant relief in symptoms. In Control group 40% cases shown some extent in symptoms relief and 60% cases shown no change in symptoms.

Table - XI : Distribution of Cases According to Vaginal Cytology (Maturity Index) before therapy and after 2 months of therapy.

Vaginal Smear Pattern	Premarin				Evalon				E2 Gel				Ovral-L				Control Group			
	Before Therapy		After 2 months		Before Therapy		After 2 months		Before Therapy		After 2 months		Before Therapy		After 2 months		Before Therapy		After 2 months	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Normal Pattern	2	20	5	50	3	30	5	50	2	20	4	40	2	20	4	40	2	20	-	-
Intermediate Pattern	4	40	1	10	3	30	1	10	3	30	1	10	2	20	1	10	2	20	3	30
Atrophic Pattern	4	40	4	40	4	40	4	40	5	50	5	50	6	60	5	50	6	60	7	70
Total	10	100	10	100	10	100	10	100	10	100	10	100	10	100	10	100	10	100	10	100

Percentage of cases of normal pattern increase from 20%-50% in premarin , 30%-50% in Evalon , 20%-40% in E_2 gel , 20%-40% in ovaral-L and 20%-0% in control group, after 2 months of therapy cases of intermediate pattern drop down from 40%-10% premarin group , 30%-10% in Evalon , 30%-10%% in E_2 gel, 20%-10% in ovaral-L and in control group rise in intermediate pattern from 20%-30%. Cases of atrophic pattern (parabasal cells) not change in absolute but no. of atrophic cells markedly reduce in after 2 months of therapy in all four group. But in control group slight rise in atrophic pattern from 60%-70%.

Table - XII : Distribution of Cases According to Vaginal Cytology (Maturity Index) before therapy and after 6 months of therapy.

Vaginal Smear Pattern	Premarin				Evalon				E2 Gel				Ovral-L				Control Group			
	Before Therapy		After 6 months		Before Therapy		After 6 months		Before Therapy		After 6 months		Before Therapy		After 6 months		Before Therapy		After 6 months	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Normal Pattern	2	20	6	60	3	30	6	60	2	20	5	50	2	20	4	40	2	20	-	-
Intermediate Pattern	4	40	3	30	2	20	4	40	3	30	5	50	2	20	6	60	2	20	3	30
Atrophic Pattern	4	40	0	0	4	40	0	0	5	50	0	0	6	60	0	0	6	60	7	70
Total	10	100	10	100	10	100	10	100	10	100	10	100	10	100	10	100	10	100	10	100

Percentage of cases of normal pattern changes from 20%-60% in premarin group, 30%-60% in Evalon , 20%-50% in E_2 gel , 20%-40% in ovral-L and 20%-0% in control group, after 6 months of therapy. Cases of intermediate pattern changes from 40%-30% in premarin group , 20%-40% in Evalon , 30%-50% in E_2 gel, 20%-60% in ovral-L and 20%-30% in control group, after 6 months of therapy. Cases of atrophic pattern markedly drop down from 40%-0% in premarin group 40%-0% in Evalon , 50%-0% in E_2 gel , 60%-0% in Ovral-L after 6 months of therapy. Control group increased atrophic pattern from 60%-70% after 6 months of observation.

Table - XIII : Distribution of Cases According to Vaginal Cytology (Maturity Index) After 2 months and 6 months of therapy.

Vaginal Smear Pattern	Premarin				Evalon				E2 Gel				Ovral-L				Control Group			
	After 2 months		After 6 months		After 2 months		After 6 months		After 2 months		After 6 months		After 2 months		After 6 months		After 2 months		After 6 months	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Normal Pattern	5	50	6	60	5	50	6	60	4	40	5	50	4	40	5	50	0	0	0	0
Intermediate Pattern	1	10	4	40	1	10	4	40	1	10	5	50	1	10	5	50	3	30	3	30
Atrophic Pattern	4	40	0	0	4	40	0	0	5	50	0	0	5	50	0	0	7	70	7	70
Total	10	100	10	100	10	100	10	100	10	100	10	100	10	100	10	100	10	100	10	100

Cytological pattern changed from 2 month of HRT to 6 months of HRT. In normal pattern changed from 50%-60% in premarin group, 50%-60% in Evalon , 40%-50% in E_2 gel , 40%-50% in ovaral-L and no change in normal pattern in control group, from 2 months to 6 months of therapy. In intermediate pattern changes occurred from 10%-40% in premarin group, 10%-40% in Evalon , 10%-50% in E_2 gel, 10%-50% in ovaral-L and control group showed no change. In atrophic patterm markedly decreased form 40%-0% in premarin 40-0% in Evalon 50%-0% in E_2 gel , 50%-0% in ovaral-L. In Control group showed no improvement.

Table - XIV : Mean Percentage Cells in Vaginal Cytology Before Therapy and After 2 months After 6 months of therapy.

Sl. No.	Drugs	Before Therapy			After 2 months of therapy			After 6 months of therapy		
		Parabasal Cells (%)	Intermediate Cells (%)	Superficial Cells (%)	Parabasal Cells (%)	Intermediate Cells (%)	Superficial Cells (%)	Parabasal Cells (%)	Intermediate Cells (%)	Superficial Cells (%)
1.	Premarin	23	38	39	9	36	55	0	33	67
2.	Evalon	12	43	45	4	36	60	0	35	65
3.	E_2 Gel	11	46	43	4	43	53	0	38	62
4.	Ovaral-L	15	50	35	5	48	47	0	42	58
5.	Control Group	16	44	40	16	47	37	18	50	32

Note :- The Desimal has been rounded off.

From the above table, it was observed that mean percentage of parabasal cell fall in different group of HRT after 2 month and 6 month of therapy.

From 30 to 9 to 0 in premarin.

From 12 to 4 to 0 in Evalon.

From 11 to 4 to 0 in E_2 gel.

From 15 to 5 to 0 in Ovaral-L.

In Control group from 16 to 16 to 18.

Intermediate cells represented

From 38 to 36 to 33 in premarin

From 43 to 36 to 35 in Evalon.

From 45 to 43 to 38 in E_2 gel.

From 50 to 48 to 42 in Ovaral-L.

In Control group 44 to 47 to 50 .

In Superficial cells increasing mean patterns

From 39 to 55 to 67 in premarin

From 45 to 60 to 65 in Evalon.

From 43 to 53 to 62 in E_2 gel.

From 35 to 47 to 58 in Ovaral-L.

In Control group showed decline in normal pattern .

From 40 to 37 to 32.

Table :XV- **Comparative evaluation of side effect of different types of HRT**

Adverse effect	Premarin		Evalon		E_2 gel		Ovral-L	
	No.	%	No.	%	No.	%	No.	%
Local								
Itching/ rashes	-	-	-	-	2	20	-	-
Systemic								
Headache	1	10	1	10	-	-	1	10
Increase weight	1	10	-	-	1	10	-	-
Nausea/ vomiting	1	10	-	-	-	-	-	-
Break though bleeding	-	-	-	-	1	10	1	10
Vaginal discharge	-	-	2	20	1	10	1	10

With E_2 gel 20% cases developed skin itching, increasing weight in 10% cases, break through bleeding in 10% cases , vaginal discharge showed 10% cases. With Premarin , 10% cases developed headache , 10% developed weight gain , nausea/vomiting deveoped in 10% cases. With Evalon , 10% cases developed headache , 20% cases developed vaginal discharge. With Ovral-L, 10% cases developed headache , 10% cases developed break through bleeding, 10% cases vaginal discharge.

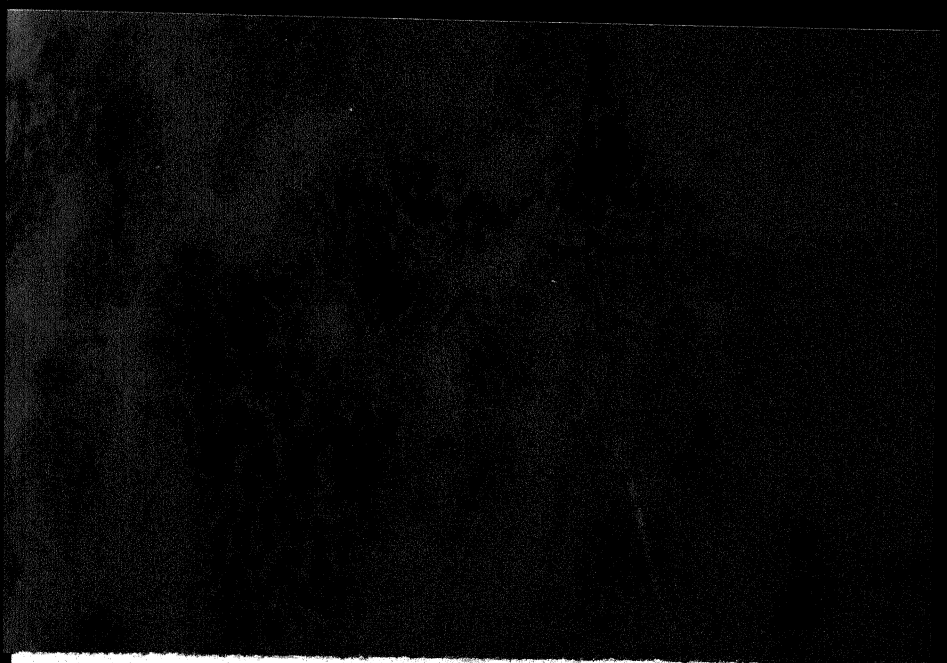


Fig-1: Vaginal smear of menopausal women showing atrophic pattern of squamous epith.

Fig-2: Vaginal smear showing parabasal and intermediate cells (menopause)

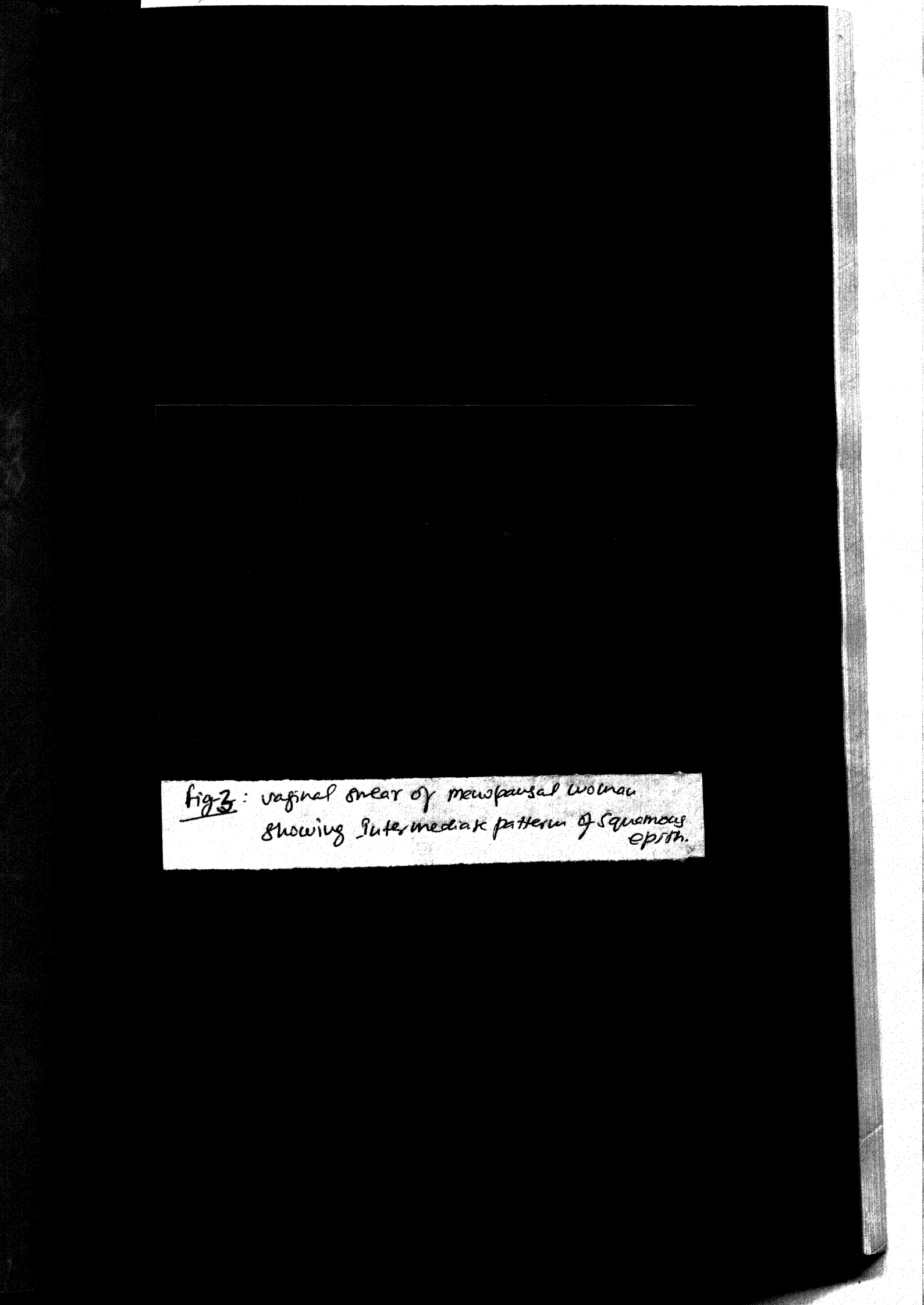
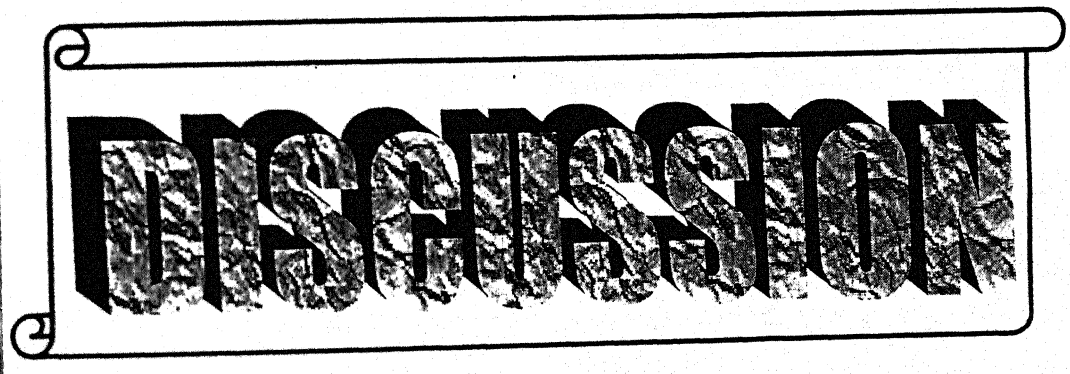


fig-3: vaginal smear of menopausal woman showing Intermediate pattern of squamous epith.

Fig-4: Vaginal smear of menopausal women showing Normal pattern of squamous epith.



DISCUSSION

Hormone replacement therapy is an issue of vital medical importance in the care of increasing of an ageing women , Who simultaneously balance professional and domestic commitment. Various formulation , combinations , route and duration of therapy exist for use. To date , oral therapy either continuously or cyclically has been the most common hormone treatment. However, The introduction of transdermal theraputic system has allowed estradiol to be administered in low doses , improving quality , tolerability and compliance while maintaining efficacy.

The present study was conducted on 50 post menopausal patient to evaluate comparative efficacy of different type of HRT (Premarin ,Evalon , E_2 gel and Ovral-L). All patient were examined thoroughly for clinical manifestations, vaginal smear pattern , serum lipoproteins, lever function test. Reevaluation of all things was done 2 months and 6 months after therapy.

Lastly comparison of all four types of HRT done with placebo therapy whether hormone therapy is effective in real sense are just as placebo therapy.

Total 50 post menopausal patients were divided into 5 groups -

A. Premarin Group.

B. Evalon Group.

C. E_2 Gel Group.

D. Ovral-L Group.

E. Control Group.

Each groups bear 10 patients.

A. Premarin Group :-

In this group 10 patients were treated with oral conjugated equine estrogen 0.625 mg per day for 3 weeks with one week off. Medroxy progesteron given 10 mg. for last 10 days per months.

B. Evalon Group :-

In this group 10 patients were treated with oral Estriol tablet 1 mg. per day for 3 week with 1 week off. Estriol is natural estrogen. Medroxy progesteron given 10 mg. for last 10 days per month.

C. E_2 Gel Group :-

In this group 10 patients were treated with transdermal 17 beta Estrediol gel. 2.5 g gel applied over for arm and Shoulder, twice a week for 3 week with one week off. Medroxy progesteron given 10 mg. for last 10 days per months.

D. Ovral-L Group :-

In this group 10 patients were treated with oral a combination of ethinyl estrediol 0.03mg. and leonorgestrel

0.15 mg., 1 tablets per day for 3 week per months with 1 week off.

Effect of HRT on Serum Lipids -

Studies have shown that serum lipids levels are significantly higher in post menopausal women. Effect of HRT on serum lipids are also significant than in age matched menopausal women which is not taken HRT (Aitken 1971 , Gustofson and svanberg 1972 , Punnonen and Rauromo 1976-80, patterson et al 1980, Notelviez et al 1983 , PEPI trial group of writing 1995 , Darling et al (1997).

In the present work serum lipid lipoproteins levels were estimated in women undergoing natural and surgical menopause.

A. Premarin - (Conjugated equine estrogen)

The mean basal level of serum cholesterol (STC), Triglyceride (STG), High Density lipoprotein (HDL) and Low Density lipoprotein (LDL) were, 216 mg/dl , 127 mg/dl , 41.1 mg/dl and 150.8 mg/dl respectively. There was significant changes in serum lipoprotein after 2 month and after 6 months, changes occurred highly significant of premarin therapy.

A ratio of basal sample to 2 month (A : B) and 6 month (A:C) and a ratio of after 2 month to 6 months (B: C) of therapy shown statistical significant (Table - IV).

A : B -

STC : $t = 3.2$, $P < 0.05$ significant.

STG : $t = 2.74$, $P < 0.05$ significant.

HDL : $t = 2.44$, $P < 0.05$ significant.

LDL : $t = 7.37$, $P < 0.01$ highly significant.

A : C -

STC : $t = 5.83$, $P < 0.01$ highly significant.

STG : $t = 5.36$, $P < 0.01$ highly significant.

HDL : $t = 8.77$, $P < 0.01$ highly significant.

LDL : $t = 10.70$, $P < 0.01$ highly significant.

B : C -

STC : $t = 6.02$, $P < 0.01$ highly significant.

STG : $t = 5.78$, $P < 0.01$ highly significant.

HDL : $t = 10.00$, $P < 0.01$ highly significant.

LDL : $t = 9.48$, $P < 0.01$ highly significant.

Initialy STC STG and HDL shown significant changed ($P<0.05$). After 2 month of therapy LDL shown highly significant changes ($P<0.01$).

B. Evalon - (Estriol)

The mean basal level of serum cholesterol (STC), Triglyceride (STG), High Density lipoprotein (HDL) and Low

Density lipoprotein (LDL) were, 205.5 mg/dl , 126 mg/dl , 38.1 mg/dl and 142.2 mg/dl respectively. There was significant changes in all above entities after two month and 6 month of evalon therapy.

A ratio of basal sample to 2 month (A : B) and 6 month (A:C) and a ratio of after 2 month to 6 months (B: C) of therapy shown statistical significant as below. (Table V)

A : B -

STC : $t = 2.74$, $P < 0.05$ significant.

STG : $t = 3.16$, $P < 0.05$ significant.

HDL : $t = 4.0$, $P < 0.01$ highly significant.

LDL : $t = 5.0$, $P < 0.01$ highly significant.

A : C -

STC : $t = 4.14$, $P < 0.01$ highly significant.

STG : $t = 8.76$, $P < 0.01$ highly significant.

HDL : $t = 14.3$, $P < 0.01$ highly significant.

LDL : $t = 12.97$, $P < 0.01$ highly significant.

B : C -

STC : $t = 7.30$, $P < 0.01$ highly significant.

STG : $t = 14.72$, $P < 0.01$ highly significant.

HDL : $t = 8.80$, $P < 0.01$ highly significant.

LDL : $t = 15.0$, $P < 0.01$ highly significant.

Initialy STC and STG shown slow changes but statistical significant ($P<0.05$). HDL and LDL shown highly significant ($P<0.01$) first 2 month of therapy.

C. ***E_2 Gel*** - (17 beta Oestradiol)

The mean basal value of (STC), (STG), (HDL) and (LDL) were, 211.4 mg/dl , 126 mg/dl , 39.8 mg/dl and 146.4 mg/dl respectively. There were significant changes shown after 2 months and 6 months of therapy.

A ratio of A : B , A:C and B: C shown statistical significant as below.(Table VI)

A : B -

STC : $t = 2.63$, $P < 0.05$ significant.

STG : $t = 2.36$, $P < 0.05$ significant.

HDL : $t = 2.87$, $P < 0.05$ significant.

LDL : $t = 5.30$, $P < 0.01$ highly significant.

A : C -

STC : $t = 4.37$, $P < 0.01$ highly significant.

STG : $t = 2.44$, $P < 0.05$ significant.

HDL : $t = 6.58$, $P < 0.01$ highly significant.

LDL : $t = 7.72$, $P < 0.01$ highly significant.

B : C -

STC : $t = 6.55$, $P < 0.01$ highly significant.

STG : $t = 2.37$, $P < 0.05$ significant.

HDL : $t = 9.72$, $P < 0.01$ highly significant.

LDL : $t = 8.00$, $P < 0.01$ highly significant.

There were significant change shown STC, HDL and LDL but STG shown significant changes not exceed P<0.05.

D. Ovral-L -

The mean basal value of (STC), (STG), (HDL) and (LDL) were, 205.8 mg/dl , 120 mg/dl , 40.5 mg/dl and 140.3 mg/dl respectively. There were significant changes shown after 2 months and 6 months of therapy.

A ratio of A : B , A : C and B : C shown statistical significant as below (Table VII)

A : B -

STC : $t = 3.09$, $P < 0.05$ significant.

STG : $t = 3.20$, $P < 0.05$ significant.

HDL : $t = 2.75$, $P < 0.05$ significant.

LDL : $t = 4.34$, $P < 0.01$ highly significant.

A : C -

STC : $t = 5.26$, $P < 0.01$ highly significant.

STG : $t = 5.43$, $P < 0.01$ highly significant.

HDL : $t = 11.93$, $P < 0.01$ highly significant.

LDL : $t = 11.47$, $P < 0.01$ highly significant.

B : C -

STC : $t = 6.44$, $P < 0.01$ highly significant.

STG : $t = 10.27$, $P < 0.01$ highly significant.

HDL : $t = 15.10$, $P < 0.01$ highly significant.

LDL : $t = 10.27$, $P < 0.01$ highly significant.

Initially STC, STG , HDL showed statistical significant at ($P<0.05$) and LDL shown significant ($P<0.01$) after 2 months of therapy.

E. Control Group - (Plecebo therapy)

The mean basal value of (STC), (STG), (HDL) and (LDL) were, 202 mg/dl , 122 mg/dl , 42.4 mg/dl and 130.4 mg/dl respectively. There were 50 ml significant changes shown after 6 months of therapy.

A ratio of basal to 2 months (A : B) and 6 months (A : C) and after 2 months to 6 months (B : C) observation on plecebo therapy changes in serum lipoprotein shown as below (Table - VIII).

A : B -

STC : $t = 2.09$, $P > 0.05$ not significant.

STG : $t = 1.00$, $P > 0.05$ not significant.

HDL : $t = 1.97$, $P > 0.05$ not significant.

LDL : $t = 2.20$, $P > 0.05$ not significant.

A : C -

STC : $t = 2.29$, $P < 0.05$ significant.

STG : $t = 1.25$, $P > 0.05$ not significant.

HDL : $t = 3.2$, $P < 0.05$ significant.

LDL : $t = 4.5$, $P < 0.01$ highly significant.

B : C -

STC : $t = 2.97$, $P < 0.05$ significant.

STG : $t = 2.17$, $P > 0.05$ not significant.

HDL : $t = 2.07$, $P > 0.05$ not significant.

LDL : $t = 3.20$, $P < 0.05$ significant.

There were no changed in serum lipoprotein first 2 month of observation. Some slight statistical significant changed in countered after 6 months of observation. (STC , HDL and LDL shown statistical significant). STG was not shown any statistical significant changed after 6 month of observation.

There were significant changed shown is serum lipoprotein (STC, STG, HDL , LDL) by all four types of HRT which are contained estrogen in different form.

Serum Cholesterol decreased significantly in all four type of HRT after 2 months significant at ($P<0.05$) and after 6 months significant at ($P<0.01$).

STG increased significant in all four type of HRT but E_2 gel shown significant only at $P<0.05$ after 2 months and after 6 months of therapy. Rest oral form of estrogen therapy shown increased STG gradually statistical significantly after 2 months $P<0.05$ and after 6 months ($P<0.01$).

HDL increased significant with all four type of HRT ,after 2 months ($P<0.05$) and after 6 months ($P<0.01$). But Evalon increased highly statistical significant changed after 2 month of therapy ($P<0.01$).

LDL declined highly statistically significant with all four type HRT after 2 months ($P<0.01$) and after 6 months ($P<0.01$) of therapy

There was significant declined in LDL/HDL ratio after 2 months and after 6 months of therapy.

	Before therapy	After 2 months	After 6 months
Premarin :	3.6 : 1	3.1 : 1	2.8 : 1
Evalon :	3.7 : 1	3.5 : 1	3.0 : 1
E_2 gel :	3.6 : 1	3.4 : 1	2.9 : 1
Ovral-L :	3.5 : 1	3.3 : 1	2.7 : 1

In Control group there were slightly changed in serum lipoprotein. STC increased slightly after 6 month of observations ($t = 2.29$; $P<0.05$). STG shown statistically in significant changed after 2 months and 6 months of observations. HDL not decreased significantly after 2 months but after 6 months of observations shown statistical significant changed ($t = 3.20$; $P < 0.05$). LDL increased gradually but not statistical significant after 2 months yet after 6 months of observations shown statistical significant changed ($P<0.01$).

Aitken (1971) showed that administration of 20-40 ug of mestronol daily in oopherectomised women was associated with significant fall in serum cholesterol and a significant rise in serum triglycerides.

Gustoson and Svanberg (1972) : an oestrogenic steroid was given for three weeks period to 6 oopherectomised women. There as significant rise in HDL and VLDl and decrease in LDL levels.

Punnonen and Rauramo (1976) showed that administration of 2 mg estradiol.valerate in oopherectomised women showed significant rise in serum phospholipids but no significant effect on cholesterol and triglyceride levels.

Patterson et al (1980) showed that there was little alterations in the mean serum cholesterol concentration and triglycerides with cyclical oestrogen but sequential oestradiol valerate and norgestrel significantly reduced the mean serum cholesterol and significant rise in serum triglyceride in post menopausal women.

Punnonen and Rauramo (1980) showd that injections of both 10 mg of oestradiol valerate and 2.5 mg of estradiol benzoate plus 10 mg estradiol thinyl propionate caused significant rise in HDL cholesterol level in bilateral oopherectomised women.

Notelovitz et al (1983) : different types and doses of oestrogen was administered in bilateral oopherectomised women. After 3 months serum cholesterol levels were unaffected by 1 and 2 mg of micronized 17 beta oestradiol or 0.625 and 1.25 mg of conjugated equine oestrogen.

Triglyceride levels were significantly elevated with conjugated oestrogen administration. A trend towards higher relative protein of high density lipoprotein and lower relative proportion of low density lipoproteins was observed in all.

The writing group for PEPI Trial (1995) It was demonstrated that there is a decreased in total cholesterol, an increasing in HDL level by about 10% , and decreased in LDL level also by about 10% on unopposed oestrogen for HRT.

Darling et al (1997) When HRT in pharma of continuous conjugated equine estrogen with medroxyprogesteron acetate 5 Mg was compare with simvastatin , both caused a similar degree increase in HDL level.

Age Incidence of Menopause

In our present study 16 case of surgical menopause (with or without oopherectomy) and 34 natural menopausal woemn.

The mean age of menopause was 44 years in the present study which includes both surgical and natural menopause. The mean age of natural menopause was 46 years in our study, which was comparable to those of Anklesaria (1995), according to that study, it was 44.35 years . But in west it is around 50.8 years.

Age of menopause is affected by type of menopause due to increased incidence of panhystrectomy at an early age incidence of menopause comes down.

Studies in India conducted by Wyon et al (1966) Randhawa et al (1987), and Kaws et al (1994) , consistently showed a lower age at menopause among Indian women as compared to those in west. Most Indian studies locate the mean age at menopause as 48 years, while those from the west reveals the same to be about 51 years (WHO Scientific group 1981). It appears to be unaffected by socio-economic status, parity, height and weight of female.

Duration of menopause :

At the time of presentation , in most of the cases average duration of menopause was 2-3 years. This finding can be explained by low socio-economic status, more of illiteracy among Indian females and ignorance about menopausal symptoms. Only when atrophic symptoms interfere with their day to day life, then they seek medical advice. In most of the cases, it was seen that duration of menopause was affected by type of menopause whether it was surgically induced or natural. In cases of surgical menopause , most of the patients presented within 2 months with symptoms of vasomotor instability. It might be due to sudden hormonal withdrawal from removal of ovary.

Menopausal Symptoms :

On pre-treatment counseling of post-menopausal females hot flushes and night sweats were seen in 25 patients (50%). Genito-utinary complaints were found in 25 patients (50%).

Psychological symptoms were seen in 46 patients (92%) and patients with late consequence of menopause were 3 patients (6%).

Mostly patients represented with 2 or 3 group of symptoms like :

Vasomotor/Urogenital	=	5	(10%).
Vasomotor/Psychological	=	20	(40%)
Urogenital/Psychological	=	15	(30%)
Late consequence/Psychological	=	3	(6%)
Vaso/Uro/Psychological	=	8	(16%)
		50	100%

(Table No. 9)

Relative frequency of post-menopausal symptoms by various workers.

S. No.	Symptoms	Western	Indian Incidence		
		studd & Barber 1992	Krishna 1995	Anklesaria 1995	Present study
1.	Hot flushes & Night sweat	78 %	33 %	30 %	50 %
2.	Urinary complaints	20 %	35 %	74 %	50 %
3.	Psychological symptoms	92 %	20 %	36 %	92 %
4.	Bony pains	48 %	25 %	20 %	6 %

From the above table , it is clear that our results are comparable to these workers in different , in different entities.

Vasomotor and psychological symptoms comparable nearly to studd (1992). Urogenital and Late consequence symptoms comparable near by Anklesaria (1995). Wide variation of our study may explained by Lack of awareness of symptoms and due to iliteracy, those patients in which have symptom of late consequence like bone pain not come to gynaecologist frequently because of those thing it may orthopaedic in origin. Vasomotor and urogenital atrophy symptoms mostly associated with phychological problem also because of disturbance in daily routine life and night sleep disturbances.

1. Premarin -

After 2 months of therapy 50% represented some extent in symptoms relief and 50% represented significant relief in symptoms. After 6 months of therapy 90% showed compelte abolition in symptom in 10% significant relief in symptoms.

2. Evalon -

After 2 months of therapy 50% represent some extent of relief in symptoms and 50% represent significant relief in symptoms. After 6 months of therapy 90% showed complete abolition in symptom in 10% significant relief in symptoms.

3. E_2 Gel -

After 2 months of therapy 40% shown some extent of relief in symptoms and 60% represent significant relief in

symptoms. After 6 months of therapy 100% showed complete abolition in symptom.

4. *Ovral-L*

After 2 months of therapy 90% represented some extent of relief in symptoms and 10% shown significant relief in symptoms. After 6 months of therapy 80% showed complete abolition in symptom and 20% shown significant relief in symptoms.

5. *Control group - (Plecebo therapy)*

After 2 months of plecebo therapy 30% represented shown extent of relief in symptoms in 70% shown no change. After 6 months of plecebo therapy 40% shown some extent in symptom relief and 60% shown no change in symptoms.

Vasomotor Symptoms -

Whitehead (1990) described a progressive decline in hot flushes with each month of cyclical estradiol therapy. 60% suppression after one month, 80% after 2 months and 90% after 3 months of cyclic treatment with transdermal estradiol.

A number of large scale studies have confirmed this clinical efficacy of transdermal estradiol (Buvat et al 1989, Eicher & Muck 1990, Errkola et al 1991 , Grall 1990 and Jaunad 1990).

According to Steingold and Laufer (1985), oral and transdermal estradiol are equally effective in the treatment of hot flushes.

In study by Kerzel (1987) in 112 patients hot flushes were completely abolished in 64% of patients and the frequency and intensity were markedly reduced in the remainders.

According to Nachtigall (1988), Randall (1988), efficay can be maintained in long term study, where vasomotor symptoms were either greatly improved or abolished in majority of patients.

Superiority of transdermal route over placebo therepay has been confirmed in relieving symptoms of vasomotor instability placebo therapy is effective in only 40% cases. This observation is supported by Laufer et al (1983) and Steingold et al (1985).

This resultcan be compared with study by Steingold and Laufer (1985), oral estrogen and transdermal estradiol both are equally effective in the treatment of hot flushes.

Urogenital Symptoms

According to Grall (1990) after 6 months of transdermal therapy, dyspareunia and urinary disorder were completely abolished in 86% and 90% of patients, respectively.

According to Janaud (1990) , Erkkola et al (1991).Transermal therapy relieved urogenital problem in upto 90% of the patients and 45-63% reduction in these symptoms in the first month of treatment with transdermal estradiol.

Khan et al (1990) reported beneficial effect of treatment with estriol therapy on urogenital symtopms.

Psychological Symptoms -

Rabe et al (1990) reviewed the effect of two months of transdermal therapy on 15,194patients and found 50% reduction in symptoms such as insomnia, irritability and depression.

Grall (1990) 75% of 2141 evaluable patients complained of Insomnia before therapy , his was reduced to 25% after 6 months of treatment with transdermal estradiol. Schleusker (1988) noted an improvement in nervousness and insomnia in 120 patients after only 2weeks of treatment.

Let Consequence Symptoms :-

Estrogen replacement therapy appears to have a direct effect on oesteoblast function (Emans SI. Grace E, Haffer FA ; Hoffer FA woods ER (1990).

A four years randomized study from the university of taxes showed for the first time on the additive effect of

intermittent cyclical etidronate and HRT on the bone mineral density in both vertebral and the hip (Jha U.P. 1997).

Vaginal Cytology :

Vaginal cytology was done routinely in every patient with post-menopausal symptom and effect of hormone replacement theapy was seen after 2 month and 6 month of therapy. In all for group - Premarin, Evalon, E_2 gel , Ovral-L and control group vaginal cytology pattern shown as below.

Normal pattern -

20% in Premarin

30% in Evalon

20% in E_2 gel

20% in Ovral-L

20% in Control group.

Intermediate Pattern -

40% in Premarin

30% in Evalon

30% in E_2 gel

20% in Ovral-L

20% in Control group.

Atrophic Pattern -

40% in Premarin

40% in Evalon

50% in E_2 gel

60% in Ovral-L

60% in Control group.

(Table -11)

These types of pattern vaginal cytology are comparable to duration of menopause. Most of the postmenopausal female showed early menopausal and intermediate pattern. This can be explained by the fact that most of the patient of our study group were between 0-5 years of duration of menopause and during this short period of menopause vaginal epithelium does not showed marked atrophic changes because there are other showeds of estrogen production in female body. Beside this , there is also and another factor that most of women were sexually active during early menopause.

According to Leibium et al 1983 women who lead an active and satisfying sexual life after menpause, appears to be less likely to develop, post menopausal atrophy than the women whose sexual life is inactive.

Effect of Hormone replacement therapy on vaginal cytology

Normal → Intermediate → atrophic pattern vaginal cytology showed gradual deprivation of estrogen in circulation. estrogen therapy changed gradually atrophic → intermediate → normal pattern. In present study all four drugs showed significant effect on vaginal cytology after 2 months and after 6 months of theapy (Table 14).

After giving hormone replacement therapy , there was marked increased in maturation of vaginal epithelium. After 2 month of therapy intermediate to normal pattern changed in premarin 30% in evalon 20% in E_2 gel 20% and ovral-L 10%. After 6 months of therapy changed from intermediate to normal pattern. In premarin 60%, in Evalon 60%, E_2 gel 50%, ovaral-L 40% and atrophic pattern to intermediate pattern after 6 months in premarin 100% , in Evalon 100% , in E_2 gel 100% , Ovaral-L 100%.

In control group vaginal cytology showed changes apparently from normal to intermediate to atrophic after 6 months of observation. (Table - XIV)

Laufer et al (1983) observed significant reduction in basal and parabasal cells, further confirmed by Pad wick et al (1985) and Pattison et al (1989).

According to Padwick et al (1985) mean percentage of basal cell fall from 40 to 0 , mean percentage of intermediate and superficial cells rose from 54 to 74 and 6 to 26 , respectively ($P<0.05$).

Laufer et al (1983) observed that the percentage of superficial cells and parabasal cells in post menopausal women treated with trnasdermal route were comparable to those in premenopausal women.

In our present study in premarin mean percentage of parabasal cell fall from 23 to 9 after 2 months of therapy and 9 to 0 after 2-6 months of therapy. In Evalon parabasal cell fall 12 to 4 after 2 months of therapy and 4-0 after 2-6 months. In E_2 gel parabasal cell for 11 to 4 after 2 months of therapy and 4 to 0 from 2 to 6 months of therapy. In ovral-L parabasal cell for 15 to 5 after 2 months of therapy and 5 to 0 from 2 to 6 months of therapy.

Side Effect of HRT in various group

Transdermal estrogen form (E_2 gel) was found to be responsible for skin reaction at site of application , in form of etching and rashes in 20% cases after 2 to 3 application but it was not very severe. This problem was solved by changing the site of application. Other side effects were.

Weight gain 10% , Break through bleeding 10% , vaginal discharge 10% (Table-15).

According to Sitrukware (1990) , Utiani (1988). Youngkins (1990), skin irritation at the site of application is most common adverse effect experienced when using the transdermal therapy.

Nachtegall (1988) reported skin irritation 14% of 133 patients receiving transdermal estradiol. There is no question of skin irritation with oral therapy.

In oral group of HRT found some GI and systemic side effect.

Premarin Group -	Headache in 10%
	Weight gain in 10%
	Nausea/vomitting in 10%
	Vaginal discharge in 10%
Evalon Group -	Headache in 10%
	Vaginal discharge in 20%
Ovral-LGroup -	Headache in 10%
	Break through bleeding 10%
	Vaginal discharge in 10%

There was no major side effect in all four group which need to discontinuation of therapy. All four drugs content low dose of estrogen which is minimized the side effect.

Transdermal estradiol therapy therapy has been shown to be at least as effective against post-menopausal symptoms as oral in all clinical trials, Furthermore it increase compliance and avoids some of the metabolic adverse effects associated with oral administration (Balfour & Heel ,Bayour & Tavish 1992 , Chetowski et al 1986 , Utian 1988).

SUMMARY AND CONCLUSION

SUMMARY AND CONCLUSION

The present study *"A comparative clinico-biochemical and cytological evaluation of different types of HRT in post menopausal women"* , was carried out in the department of Obstetrics and Gynaecology , in collaboration with the department of pathology and department of medicine (Lipid laboratory unit) , M.L.B. Medical College , Jhansi.

A total 50 patients with more than 6 month of amenorhea are Panhysterectomy at list one month back with one are more than one climacteric symptoms were selected from out patients department of Gynaecology. History of individual climacteric symptoms were taken in detail to judge the severity of symptoms and efficacy of different type of therapy on different symptoms. All patients were examined thoroughly to find out any general or systemic dysfunction and to rule out any absolute contra indication, such patients were excluded from study. Specific investigations such as serum lipid lipoproteins vaginal cytology was done prior to therapy to evaluate the comparative effect of HRT on serum lipids in vaginal cytology after 2 months and 6 months of therapy.

Patients divided in to five groups

1. ***Premarin :-***

Patients treated with oral conjugated equine estrogen in doses of 0.625 ml./day per 6 months in cyclical manner

2. ***Evalon -***

Patients treated with oral Estriol in doses of 1 ml./day for 6 months in cyclical manner.

3. ***E_2 gel -***

Patients treated with 17 beta estrediol in doses of 2.5 gm. of gel (0.06% w/w) twice a week on cyclical manner for 6 months.

4. ***Ovral-L -***

Patients treated with a combination of Ethynil estrediol 0.03 mg. and leonargestrel 0.15 mg. for 6 months in cyclical manner.

5. ***Control Group -***

A plecebo tablet in form of calcium 1000 ml/day in this group of patient for six months.

The finding are summarized asfollows :-

1. Age of patient selected for study was between 40-70 years. Maximum number of cases were 46 - 50 years.

2. The mean age of natural menopause represented by patients in our study was 46 years.

3. Duration of menopause which is selected for study were 6 months to 20 years.

Serum lipid lipoprotein -

1. Mean basal value of serum total cholesterol , Serum triglyceride, High density lipoprotein and low density lipoprotein in mg/dl. of all five group as below :

	STC	STG	HDL	LDL
Premarin	216	217	41.1	150.8
Evalon	205	126	38.1	142.2
E_2 gel	211.1	176	35.8	146.4
Ovral-L	205.8	120	40.5	140.3
Control group	202	122	42.4	130.4

2. *Serum Cholesterol* :- Serum cholesterol decreased statistically significant by all four types of HRT after 2 months ($P<0.05$) and after 6 months highly significant ($P<0.01$).

3. *Serum triglyceride* :- Serum triglyceride increased statistically significant with all type of HRT after 2 months ($P<0.05$) and after 6 months premarin , Evalon and Ovaral-L increased highly statistically significant ($P<0.01$) but E_2 gel only significant at ($P<0.05$).

4. *High Density Lipoprotein* :- HDL increased statistically significant with all four type of HRT after 2 months ($P<0.05$) and after 6 months ($P<0.01$). But with Evalon HDL increased highly significant in 2 months of therapy ($P<0.01$).

5. *Low Density Lipoprotein* :- Declined highly statically significant with all four type of HRT after 2 month and 6 month ($P<0.01$) of therapy.

6. *Control Group (Plecebo Therapy)* :-
   - STC slightly increased after 6 month ($t = 2.29$, $P<0.05$).
   - STG showed statically in-significant changes after 2 month and 6 month of observation.
   - HDL decreased statistically significant after 6 month of observation ($P<0.05$).
   - LDL increased gradually but so slight statistically significant after 6 month of observation ($P<0.05$).

Menopausal Symptoms :-

1. Total 50% cases presented with vasomotor symptoms , 50% cases presented with urogenital symptom, 92% cases showed psychological complaint and 6% cases presented with late consequences .
2. *Drug effective on symptoms* :-
   - *Premarin* :- After 2 months of therapy 50% cases show some extent in symptoms relief and 50%

showed significant symptom relief. After 6 months of therapy 90% cases showed complete abolition of symptoms and 10% showed significant relief in symptoms.

- *Evalon* :- After 2 month of therapy 50% cases showed some extent in symptom relief and 50% cases showed significant in symptoms relief. After 6 months of therapy 90% cases showed complete abolition and 10% cases showed significant relief in symptom.

- *E_2 Gel* :- After 2 month of therapy 40% cases showed some extent in symptom relief and 60% showed significant in symptoms relief after 6 months of therapy 100% cases showed complete abolition in symptom.

- *Ovral-L* :- After 2 month of therapy 90% cases showed some extent in symptom relief and 20% cases showed significant in symptoms relief. After 6 months of therapy 80% cases showed complete abolition and 20% cases showed significant relief in symptom.

- *Control Group (Plecebo Therapy)* :- After 6 month of plecebo therapy 40% cases showed some extent in symptom relief.

3. E_2 gel (Transdermal therapy) showed best and early effect on system relief. 90% significant relief after 2 months and after 6 months 100% complete abolition of symptoms.
4. Evalon and premarin showed same effect on symptom relief. Ovaral -L take more time for significant symptoms relief.

5. First symptoms responsed by HRT earlier is vasomotor and then psychological.

Vaginal cytology -

1. All four drugs showed equally effect on vaginal cytology pattern. Pattern changed from atrophic → intermediate → superficial pattern after 6 month of therapy.

2. All four types of HRT showed significant changed into maturation indeex of vaginal cytology.

   - *Premarin* :- Mean maturation index changed from 23/38/39 to 9/36/55 to 0/33/67 after 2 month and after 6 months of therapy, respectively.
   - *Evalon* :- Mean maturation index changed from 12/43/45 to 4/36/60 to 0/35/65 after 2 month and after 6 months of therapy, respectively.

- *E_2 gel* :- Mean maturation index changed from 11/46/43 to 4/43/53 to 0/38/62 after 2 month and after 6 months of therapy, respectively.

- *Ovral-L* :- Mean maturation index changed from 15/50/35 to 5/48/47 to 0/42/58 after 2 month and after 6 months of therapy, respectively.

- *Control Group* :- Mean maturation index changed from 16/44/40 to 16/47/37 to 18/50/32 after 2 month and after 6 months of observations. respectively.

Side Effect :-

1. E_2 gel showed some skin irritation in 2 patients which was not marked.

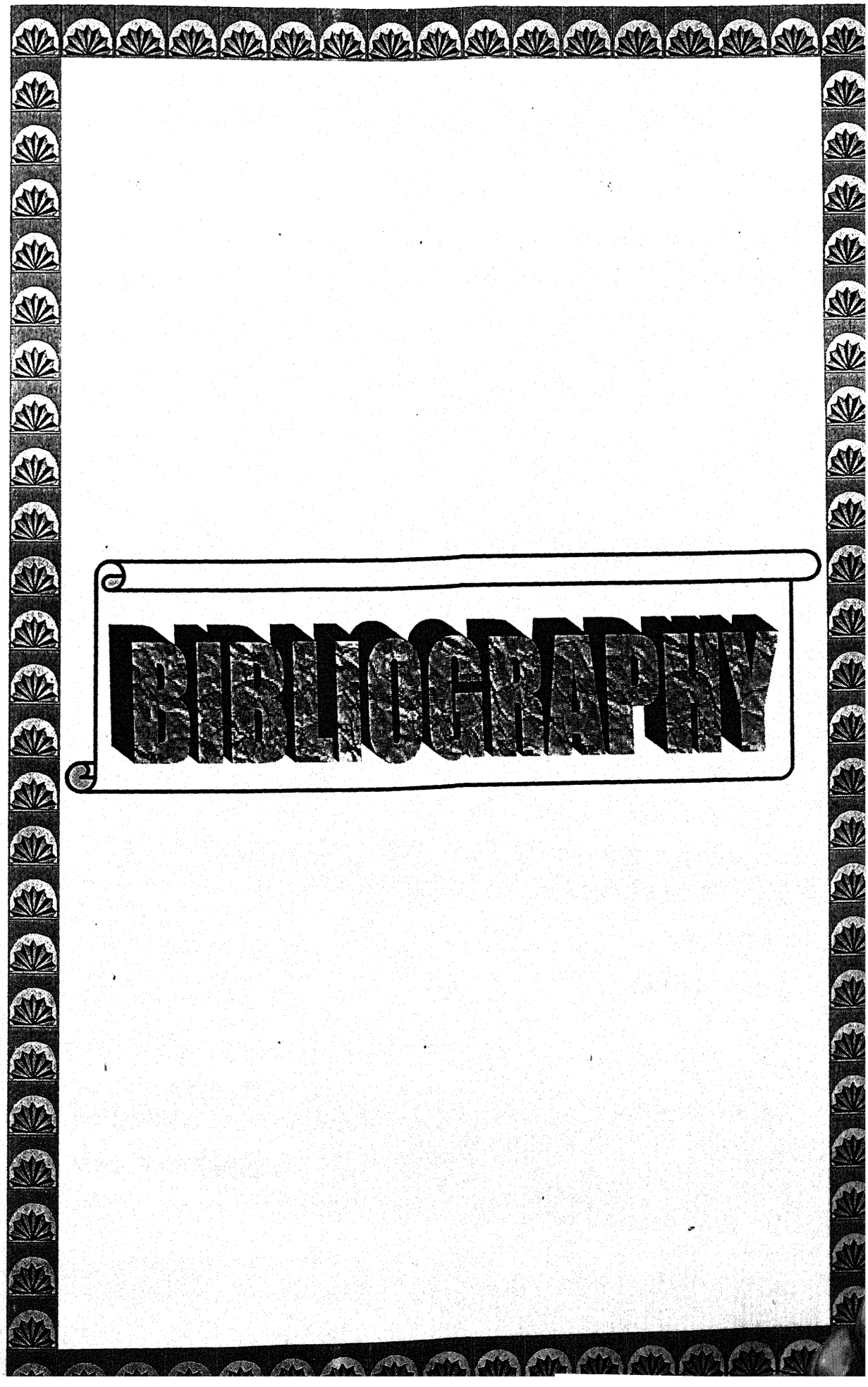
2. All four drug showed mild side effect on local and systemic but which is very mild and tolerable

Thus conclude that HRT is essential for menopausal women (surgical or natural) not only for early symptom but also prophylaxes for late consequence such as cardiovascualr disease and osteoporosis. HRT compulsory for women goes to surgical menopause.

On comparing from beneficial effect on serum lipid lipoprotein (STC, STG, HDL and LDL) all four drug are more or

less equally effective. On climacteric symptoms all four drug are significantly effective , but E_2 gel showed some early and significant effective and also showed less side effect , it is may due to low dose of estrogen content than others.

On vaginal cytology changed parabasal cells to superficial cells all four drugs are equally significantly effective.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